

Causes of Death and Factors Associated with Early Death Among Human Immunodeficiency Virus (HIV)-Infected Persons in Singapore: Pre-Highly Active Antiretroviral Therapy (HAART) and Peri-HAART

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Abstract

Introduction: Highly active antiretroviral therapy (HAART) has greatly changed the epidemiology of human immunodeficiency virus (HIV) mortality. The aim of this study is to compare the causes of death and factors associated with early death in HIV-infected persons in the pre- and peri-highly active antiretroviral therapy (HAART) periods. **Materials and Methods:** We conducted a retrospective review of 483 HIV-infected persons who were diagnosed with HIV from 1985 to 2000, and had died within 5 years of the diagnosis. We examined the temporal change in the primary causes of death between those who were diagnosed in the pre-HAART (1985 to 1995) and peri-HAART (1996 to 2000) periods, and compared the demographic and clinical characteristics of the 2 groups. **Results:** During the peri-HAART period, HIV encephalopathy, cryptococcal meningitis, and lymphoma were no longer the leading causes of death. Opportunistic infections remained important causes of death. Early deaths from the peri-HAART period were older (60 years and above) at diagnosis (Adj OR 7.50; 95% CI, 1.78 to 31.58), more likely to be divorced (Adj OR 5.05, 95% CI, 1.96 to 13.02) and tended to have a low baseline CD4 cell count of <50 cells/uL (Adj OR 2.18, 95% CI, 1.14 to 4.16), and were more likely to have received HAART (Adj OR 5.19; 95% CI, 2.22 to 12.12) than early deaths from the pre-HAART period. **Conclusion:** In the peri-HAART era, HIV-infected persons who died within 5 years of diagnosis were those who were older (≥ 60 years), divorced, or who presented with very late-stage disease (CD4 <50) at diagnosis. More targeted public health interventions, such as targeted public health messages and outreach to increase access to HIV testing and treatment should be developed for these subpopulations.

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Key words: Early mortality, Highly active antiretroviral therapy, Human immunodeficiency virus, Singapore

Introduction

Since the first case of human immunodeficiency virus (HIV) was diagnosed in Singapore in May 1985,¹ a total of 4845 cases and 1389 HIV/acquired immune deficiency syndrome (AIDS) deaths have been reported as of December 2010.² With the introduction of highly active antiretroviral therapy (HAART), AIDS diagnoses declined by 45% and deaths by 63% from 1995 to 1998 in the United States, but remained fairly stable from 1999 to 2008.³ Similar trends have been observed in other developed countries in North America, Europe and Asia.⁴⁻¹⁵ In Singapore, although there has been a decline in the overall mortality among HIV-

infected persons in the peri-HAART era, the proportion of deaths attributable to AIDS-related infections remain high.^{16,17} In contrast, the leading causes of death in most developed countries were non AIDS-related malignancy, cardiovascular and liver diseases.¹⁸⁻²³

Although older age at diagnosis and baseline CD4 cell counts have been identified as predictors for HIV progression to AIDS in Singapore in both the pre- and peri-HAART eras,²⁴ factors associated with early death of HIV-infected persons in the 2 periods have not been examined.

We describe the epidemiology of HIV/AIDS deaths in the first 20 years (1985 to 2005) of the epidemic in Singapore,

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and compared factors associated with early death among those who were diagnosed in the pre-HAART (1985 to 1995) and peri-HAART (1996 to 2000) periods.

Materials and Methods

Our study population was systematically selected from the cohort of HIV-infected persons who were treated at the Communicable Disease Centre (CDC) at Tan Tock Seng Hospital, Singapore's national referral centre for HIV/AIDS. Under the Infectious Disease Act in Singapore, all HIV infections are notified to the Ministry of Health. Following which, HIV-infected persons are referred to CDC for medical care. In 1987, antiretroviral monotherapy was first prescribed to patients in the Centre. In 1996, the first protease inhibitor (saquinavir) became commercially available. This marked the transition from the pre-HAART to HART period in Singapore. However, the use of HAART as the initial antiretroviral regimen was not consistent, due to its high costs. HAART is a treatment regimen comprising a non-nucleoside reverse transcriptase inhibitor or protease inhibitor, for at least 3 months.

We conducted a retrospective case review of HIV-infected persons who were diagnosed between 1985 and 2000, and died in CDC between 1985 and 2005. We categorised our study population into 2 groups: (i) Pre-HAART persons with a HIV diagnosis between 1985 and 1995; and (ii) Peri-HAART persons with a HIV diagnosis between 1996 and 2000. We included all HIV-infected persons who had died within 5 years of HIV diagnosis. Persons who were neither Singapore citizens nor permanent residents were excluded from the study. Data collection included socio-demographic details, HIV-associated condition(s) at the time of diagnosis, baseline serologies and CD4 counts, all antiretroviral therapies received, and the primary cause of death. Three medically-trained research assistants extracted data from the medical records using a standard form. The cause of death was ascertained through careful screening of death certificates, laboratory results, and clinical information. Serologies and CD4 counts were determined from laboratory test results. Due to the limited availability of antiretroviral drugs during the study period, a patient is deemed to have received HAART, if the treatment regimen included a nucleoside reverse transcriptase inhibitor as the backbone and contained either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. The study was approved by the domain-specific ethics review board of the National Healthcare Group to which the hospital belonged (NHG DSRB B/04/318).

Statistical Analysis

We examined the temporal change in the primary causes

of death between the pre-HAART and peri-HAART periods, and compared the demographic and clinical characteristics of early deaths in the 2 groups. Differences in the proportion of various demographic and clinical characteristics were examined using χ^2 statistics with Yate's correction or Fisher's exact test. For the multivariable analysis, variables were selected based on our literature review and prior knowledge of potential confounders, and using the forward selection and backward elimination methods. The best model was selected using the likelihood ratio chi-square test. Unadjusted and adjusted odds ratios and 95% confidence intervals (CI) were computed for the 2 time periods (pre-HAART and peri-HAART). Data were analysed with Stata Release 11.0 (Stata Corporation, College Station, Texas, USA), and all statistical tests were performed at 5% level of significance.

Results

A total of 483 HIV-infected persons who were diagnosed with HIV from 1985 to 2000, and had died within 5 years of the diagnosis, were included in the study. Of these, there were 174 (36%) from the pre-HAART period and 309 (64%) from the peri-HAART period. The study population was predominantly male (>90%). This was comparable to the HIV-infected population in Singapore during the same period.

Among the early deaths from the pre-HAART period, the leading causes of death were pneumonia, disseminated mycobacterium avium complex (MAC), HIV encephalopathy, cerebral toxoplasmosis, disseminated cytomegaloviral (CMV) disease, cryptococcal meningitis, lymphoma, and *pneumocystis carinii* pneumonia (PCP) (Table 1). Some of the deaths from pneumonia may be attributable to PCP, due to the reluctance of diagnostic bronchoscopy use and hence the underdiagnosis of PCP during the pre-HAART period. For the early deaths in the peri-HAART period, pneumonia and disseminated MAC remained the top 2 primary causes of death. HIV encephalopathy, cryptococcal meningitis, and lymphoma were not amongst the leading causes of death. However, opportunistic infections such as disseminated CMV disease, PCP and cerebral toxoplasmosis continued to be among the top 5 causes of death in HIV-infected persons diagnosed in the peri-HAART period (Table 1). Death from these HIV encephalopathy, cryptococcal disease, lymphoma, and Kaposi's sarcoma was significantly higher among early deaths in pre-HAART (14%) compared to the peri-HAART period (6%) (Adj OR 2.62, 95%CI 1.38 to 4.97, $P = 0.003$), even after accounting for HAART. Whilst two-thirds of the patients who died during the pre-HAART period were aged below 40 years at diagnosis, only one-third of those from the peri-HAART period were from the same age group (Table 2). HIV-infected persons who were diagnosed in

Table 1. Top 5 Causes of Death Among Early Deaths Diagnosed in the Pre-HAART and Peri-HAART Periods

Pre-HAART (1985 to 1995)					Peri-HAART (1996 to 2000)				
Rank	Primary Cause of Death	No.	%	95% CI	Rank	Primary Cause of Death	No.	%	95% CI
1	Pneumonia & bronchopneumonia	38	21.8	15.94 to 28.72	1	Pneumonia & bronchopneumonia	66	21.4	16.92 to 26.36
2	AIDS- disseminated mycobacterium avium complex	10	5.7	2.79 to 10.32	2	AIDS- disseminated mycobacterium avium complex	25	8.1	5.30 to 11.71
3	AIDS-HIV encephalopathy	7	4.0	1.63 to 8.11	3	Disseminated CMV	16	5.2	2.99 to 8.27
3	AIDS-cerebral toxoplasmosis	7	4.0	1.63 to 8.11					
4	Disseminated CMV	6	3.4	1.28 to 7.35	4	PCP/pneumocystosis	14	4.5	2.50 to 7.49
5	AIDS-cryptococcal meningitis	5	2.9	0.94 to 6.58	5	AIDS-cerebral toxoplasmosis	10	3.2	1.56 to 5.87
5	Lymphoma	5	2.9	0.94 to 6.58					
5	PCP/pneumocystosis	5	2.9	0.94 to 6.58					

AIDS: acquired immune deficiency syndrome; CMV: cytomegaloviral disease; HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; PCP: *pneumocystis carinii* pneumonia

Table 2. Comparison of the Demographic and Clinical Characteristics of Early Death Among HIV-Infected Persons Diagnosed in the Pre-HAART and Peri-HAART Periods

	Pre-HAART		Peri-HAART	
	No.	%	No.	%
Gender (N = 483)				
Male	163	(93.7)	284	(91.9)
Female	11	(6.3)	25	(8.1)
Total	174	(100.0)	309	(100.0)
Age at diagnosis (years) (N = 483)				
<30	36	(20.7)	31	(10.0)
30 to 39	80	(46.0)	99	(32.0)
40 to 49	39	(22.4)	105	(34.0)
50 to 59	13	(7.5)	28	(9.1)
60+	6	(3.5)	46	(14.9)
Total	174	(100.0)	309	(100.0)
Ethnic group (N = 483)				
Chinese	141	(81.0)	266	(86.1)
Malay	20	(11.5)	22	(7.1)
Indian	7	(4.0)	15	(4.9)
Others	6	(3.5)	6	(1.9)
Total	174	(100.0)	309	(100.0)
Marital status (N = 464)				
Single	112	(69.6)	143	(47.2)
Married	39	(24.2)	108	(35.6)
Divorced	8	(5.0)	39	(12.9)
Separated	1	(0.6)	2	(0.7)
Widowed	1	(0.6)	11	(3.6)
Total	161	(100.0)	303	(100.0)

Table 2. Comparison of the Demographic and Clinical Characteristics of Early Death Among HIV-Infected Persons Diagnosed in the Pre-HAART and Peri-HAART Periods (Con't)

	Pre-HAART		Peri-HAART	
	No.	%	No.	%
Employment status (N = 398)				
Employed	101	(67.8)	138	(55.4)
Retired	2	(1.3)	1	(0.4)
Unemployed	43	(28.9)	104	(41.8)
Student	2	(1.3)	1	(0.4)
Housewife	1	(0.7)	5	(2.0)
Total	149	(100.0)	249	(100.0)
Baseline CD4 count, cells/uL (N = 468)				
>200	36	(21.4)	43	(14.3)
50 to 200	56	(33.3)	68	(22.7)
<50	76	(45.2)	189	(63.0)
Total	168	(100.0)	300	(100.0)
HIV-associated condition at diagnosis (N = 483)				
No	109	(62.6)	165	(53.4)
Yes	65	(37.4)	144	(46.6)
Total	174	(100.0)	309	(100.0)
Baseline toxoplasma Ig G (N = 483)				
Negative	148	(85.1)	270	(87.4)
Positive	26	(14.9)	39	(12.6)
Total	174	(100.0)	309	(100.0)
Baseline cryptococcal Ig G (N = 483)				
Negative	166	(95.4)	294	(95.2)
Positive	8	(4.6)	15	(4.9)
Total	174	(100.0)	309	(100.0)

Table 2. Comparison of the Demographic and Clinical Characteristics of Early Death Among HIV-Infected Persons Diagnosed in the Pre-HAART and Peri-HAART Periods (Con't)

	Pre-HAART		Peri-HAART	
	No.	%	No.	%
Baseline VDRL (N = 483)				
Negative	160	(92.0)	283	(91.6)
Positive	14	(8.1)	26	(8.4)
Total	174	(100.0)	309	(100.0)
Antiretroviral therapy (N = 483)				
No treatment	115	(66.1)	187	(60.5)
NRTI only	49	(28.2)	62	(20.1)
HAART	10	(5.8)	60	(19.4)
Total	174	(100.0)	309	(100.0)

HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; NRTI: nucleoside reverse transcriptase inhibitor; VDRL: venereal disease research laboratory

the peri-HAART period and died within 5 years were 9 times as likely to be aged 60 years and above, compared to those diagnosed in the pre-HAART period (Unadj OR 8.90; 95% CI, 3.35 to 23.65) (Table 3).

Chinese was the leading ethnic group amongst early deaths during both periods. Although the majority of the early HIV deaths during both periods were single, married persons comprised 39/161 (24.2%) of those from the pre-HAART period and 108/303 (35.6%) of those from the peri-HAART period. Study subjects from the peri-HAART period were 4 times as likely to be divorced as those from the pre-HAART period (Unadj OR 3.82, 95% CI, 1.72 to 8.50) (Tables 2 and 3). In terms of employment status, a significantly larger proportion (41.8%) of the patients from the peri-HAART period was unemployed compared to the pre-HAART period (28.9%) (Unadj OR 1.77, 95% CI, 1.14 to 2.72) (Tables 2 and 3).

The baseline clinical characteristics of the patients are

Table 3. Univariate Analyses of Demographic and Clinical Factors Associated with Early HIV Death in the Peri-HAART Period Compared with Early HIV Death in the Pre-HAART Period

	Unadjusted OR	95% CI	P value
Demographic Characteristics			
Gender			
Male	1.00		
Female	1.30	0.63 to 2.72	0.5
Age at diagnosis (years)			
<30	1.00		<0.001
30 to 39	1.44	0.82 to 2.52	0.2
40 to 49	3.13	1.71 to 5.72	<0.001
50 to 59	2.50	1.11 to 5.65	0.03
60+	8.90	3.35 to 23.65	<0.001
Ethnic group			
Chinese	1.00		0.3
Malay	0.58	0.31 to 1.10	0.1
Indian	1.14	0.45 to 2.85	0.8
Others	0.53	0.17 to 1.67	0.3
Marital status			
Single	1.00		<0.001
Married	2.17	1.39 to 3.37	0.001
Divorced	3.82	1.72 to 8.50	0.001
Separated	1.57	0.14 to 17.50	0.7
Widowed	8.62	1.10 to 67.73	0.04
Employment status			
Employed	1.00		0.04
Retired	0.37	0.03 to 4.09	0.4
Unemployed	1.77	1.14 to 2.74	0.01
Student	0.37	0.03 to 4.09	0.4
Housewife	3.66	0.42 to 31.80	0.2

summarised in Tables 2 and 3. Twenty-one percent of those diagnosed in the pre-HAART period had baseline CD4 cell counts >200 cells/uL, compared with just 14% of those in the peri-HAART period. Those from the peri-HAART period were twice as likely as those from the pre-HAART period to have a CD4 cell count <50 (Unadj OR 2.08, 95% CI, 1.24 to 3.49). Almost half (46.6%) of those diagnosed during the peri-HAART period already had an HIV-associated condition at diagnosis. These subjects were 1.5 times as likely to have such a condition as subjects from the earlier period (Unadj OR 1.46, 95% CI, 1.00 to 2.14). Baseline values of antibodies to toxoplasma and cryptococcus, and results of Venereal Disease Research Laboratory (VDRL) and hepatitis B surface antigen tests, were not very different between the 2 groups.

As expected, subjects from the peri-HAART period were 4 times as likely to be on HAART (i.e. a regimen containing either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor) (Unadj OR 3.69, 95% CI, 1.82 to 7.49). However, in spite of the availability of HAART,

only 19.4% of the early deaths in the peri-HAART period received HAART therapy.

After adjusting for the effect of other factors, being at an older age of 60 years and above at diagnosis (Adj OR 7.50, 95% CI, 1.78 to 31.58), being divorced (Adj OR 5.05, 95% CI, 1.96 to 13.02), having a low baseline CD4 cell count of <50 cells/uL (Adj OR 2.18, 95% CI, 1.14 to 4.16), and receipt of HAART (Adj OR 5.19, 95% CI, 2.22 to 12.12) remained significantly associated with early deaths in the peri-HAART period compared to early deaths in the pre-HAART period (Table 4).

Discussion

Our data showed that the advent of HAART had substantially changed the epidemiology of HIV mortality in Singapore. During the pre-HAART period, HIV encephalopathy, cryptococcal meningitis, and lymphoma were among the leading causes of death in HIV-infected persons who died within 5 years of their HIV diagnoses.

Table 3. Univariate Analyses of Demographic and Clinical Factors Associated with Early HIV Death in the Peri-HAART Period Compared with Early HIV Death in the Pre-HAART Period (Con't)

	Unadjusted OR	95% CI	P value
Clinical Characteristics			
Baseline CD4 count, cells/uL			0.001
>200	1.00		
50 to 200	1.02	0.58 to 1.79	1.0
<50	2.08	1.24 to 3.49	0.005
HIV-associated condition at diagnosis			
No	1.00		
Yes	1.46	1.00 to 2.14	0.05
Baseline toxoplasma Ig G			
Negative	1.00		
Positive	0.82	0.48 to 1.40	0.5
Baseline cryptococcal Ig G			
Negative	1.00		
Positive	1.06	0.44 to 2.55	0.9
Baseline VDRL			
Negative	1.00		
Positive	1.05	0.53 to 2.07	0.9
Hep Bs Ag			
Negative	1.00		
Positive	0.70	0.37 to 1.33	0.3
Antiretroviral therapy			<0.001
No treatment	1.00		
NRTI only	0.78	0.50 to 1.21	0.3
HAART	3.69	1.82 to 7.49	<0.001

HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; NRTI: nucleoside reverse transcriptase inhibitor; VDRL: venereal disease research laboratory

Table 4. Multivariate Analysis of Demographic and Clinical Factors Associated with Early HIV Death in the Peri-HAART Period Compared with Early HIV Death in the Pre-HAART Period

	Adjusted OR	95% CI	P value
Age at diagnosis (years)			
<30	1.00		
30 to 39	1.13	0.55 to 2.30	0.7
40 to 49	2.10	0.99 to 4.45	0.05
50 to 59	0.77	0.26 to 2.34	0.6
60+	7.50	1.78 to 31.58	0.006
Marital status			
Single	1.00		
Married	1.94	1.10 to 3.40	0.02
Divorced	5.05	1.96 to 13.02	0.001
Widowed	2.29	0.25 to 21.42	0.5
Separated	1.52	0.10 to 24.31	0.8
Baseline CD4 count, cells/uL			
>200	1.00		
50 to 200	0.69	0.34 to 1.42	0.3
<50	2.18	1.14 to 4.16	0.02
Antiretroviral therapy			
No treatment	1.00		
NRTI only	0.95	0.56 to 1.64	0.9
HAART	5.19	2.22 to 12.12	<0.001

HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; NRTI: nucleoside reverse transcriptase inhibitor

These HIV-associated diseases were no longer among the leading causes of early deaths in the peri-HAART era. Compared to early mortality in the peri-HAART period, early mortality in the pre-HAART period was 2.6 times as likely to be attributable to HIV encephalopathy, cryptococcal disease, lymphoma and Kaposi's sarcoma, after accounting for HAART. This suggests changing HIV disease epidemiology over the 2 periods. However, opportunistic infections including PCP continued to be among the top 5 primary causes of death. Although some studies have shown that no deaths were attributed to PCP among HIV-infected persons in the HAART era,²² others have shown that PCP remained an important cause of death.^{18,25,26} Almost one-third of patients in the TREAT Asia HIV Observational Database (TAHOD), with appropriate indications, did not receive PCP prophylaxis. Patients who did not receive prophylaxis were 10 times more likely to die than those who received prophylaxis.²⁶ However, despite marked improvements in the prevention of many infections, numerous studies have observed that infections remain the leading cause of death among HIV-infected persons.^{9,22} Our findings are consistent with this observation. One reason why such opportunistic infections were common in our early deaths in the peri-HAART period could be that the majority (80.6%) of them had not received HAART therapy.

This was largely due to financial reasons.

Our study population included HIV-infected persons who died within 5 years of diagnosis. They represent an important subpopulation of HIV-infected persons who had a poor 5-year survival outcome. Early mortality in the peri-HAART period (327.7 early deaths per 1000 HIV-infected persons) was 30% lower than that in the pre-HAART period (415.3 early deaths per 1000 HIV-infected persons) (OR 0.69, 95% CI, 0.57 to 0.83, $P = 0.0001$) (unpublished data). The peri-HAART group was 5 times as likely as the pre-HAART group to have received HAART (Adj OR 5.19, 95% CI, 2.22 to 12.12), after adjusting for age at diagnosis, marital status and baseline CD4 cell count. However, compared to the pre-HAART group, the peri-HAART group was twice as likely to have a low baseline CD4 cell count of <50 cells/uL (Adj OR 2.18, 95% CI, 1.14 to 4.16). The peri-HAART group also tended to be older in age at diagnosis and were more likely to be divorced. A previous study has demonstrated that older age at diagnosis and low baseline CD4 cell counts were predictors of progression to AIDS.²⁴ Hence, it is not surprising that these same factors were significantly associated with early death in the peri-HAART group, after controlling for the effect of HAART.

Our study has several limitations. Firstly, it is a

retrospective study of deaths among HIV-infected persons. Hence, we are unable to examine predictors for HIV mortality in the pre-HAART and peri-HAART periods. Nonetheless, our study has identified important demographic and clinical factors which differ between early deaths in the pre-HAART and peri-HAART periods. Our study's objective was not to investigate the effect of HAART on early mortality, but rather to compare factors associated with early mortality between the pre-HAART and peri-HAART periods. Compared to the early deaths in the pre-HAART period, early deaths in the peri-HAART period tended to be HIV-infected persons who were aged 60 and above at diagnosis, or who were divorced, or who sought treatment late. Although general health educational messages on HIV are widely disseminated in Singapore, more can be done to tailor public health interventions to the older segment of the population, to improve their access to HIV testing and treatment.

Secondly, our study included only deaths that occurred in CDC. There could be selection bias introduced into our study, if HIV-infected persons who died outside of CDC were socio-demographically and clinically different from those who died in CDC. However, any selection bias present is likely to be very small, as the majority of HIV-infected persons in Singapore had died in CDC (unpublished data).

Conclusion

In summary, we observed a temporal change in the leading causes of death among HIV-infected persons from the pre-HAART period to the peri-HAART period. Although early mortality from HIV-associated diseases had reduced in the peri-HAART period, early mortality from opportunistic infections remained the same. In the peri-HAART era, HIV-infected persons who died within 5 years of diagnosis were those who were older (≥ 60 years), divorced, or who presented with very late-stage disease ($CD4 < 50$) at diagnosis. More targeted public health interventions, such as targeted public health messages and outreach to increase access to HIV testing and treatment, should be developed for these subpopulations.

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