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HIV infection associated with lower utilization of hospice care services during end-of-life treatment: A nationwide cohort study

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Complete List of Authors:	Chan, Shang-Yih; Taipei City Hospital Yangming Branch, Department of Internal Medicine; National Taipei University of Nursing and Health Sciences, Department of Health Care Management Lai, Yun-Ju; National Taipei University of Nursing and Health Sciences, Department of Health Care Management; Puli Branch of Taichung Veterans General Hospital, Department of Internal Medicine Ko, Ming-Chung ; Taipei City Hospital, Department of Urology; National Taipei University of Nursing and Health Sciences, Department of Health Care Management Chen, Yu-Yen ; Taichung Veterans General Hospital; Chung Shan Medical University Tsai, Yi-Fan; Yangming Branch, Department of Nursing; Taipei Medical University Hsu, Li-Fei; National Taiwan University Ku, Po-Wen; National Chung Hsing University, Graduate Institute of Sports and Health Chen, Li-Jung; National Taiwan University of Sport, Department of Exercise Health Science Chuang, Pei-Hung ; Taipei Association of Health and Welfare Data Science Chen, Chu-Chieh ; National Taipei University of Nursing and Health Sciences Yen, Yung-Feng; Taipei City Hospital Yangming Branch; National Yang Ming Chiao Tung University, Institute of Public Health
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Title: HIV infection associated with lower utilization of hospice care services during end-of-life treatment: A nationwide cohort study

Shang-Yih Chan[a,b,c,#], Yun-Ju Lai[b,d,e,f,#], Ming-Chung Ko[b,g,#], Yu-Yen Chen[d,h,i,j], Yi-Fan Tsai[k,l,m], Li-Fei Hsu[n], Po-Wen Ku[o], Li-Jung Chen[f], Pei-Hung Chuang[p], Chu-Chieh Chen[b], Yung-Feng Yen[b,c,h,q,s*]

[a]Department of Internal Medicine, Taipei City Hospital, Yangming Branch, Taipei, Taiwan

[b]Department of Health Care Management, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan

[c]University of Taipei, Taipei, Taiwan

[d]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

[e]Division of Endocrinology and Metabolism, Department of Internal Medicine, Puli Branch of Taichung Veterans General Hospital, Nantou, Taiwan

[f]Department of Exercise Health Science, National Taiwan University of Sport, Taichung, Taiwan

[g]Department of Urology, Taipei City Hospital, Taipei, Taiwan

[h]Institute of Public Health, National Yang Ming Chiao Tung University, Taipei,

Taiwan

[i]Department of Ophthalmology, Taichung Veterans General Hospital, Taichung, Taiwan

[j]School of Medicine, Chung Shan Medical University, Taichung, Taiwan

[k]Department of Nursing, Taipei City Hospital, Yangming Branch, Taipei, Taiwan

[l]School of Nursing, Taipei Medical University, Taipei, Taiwan

[m]Department of Allied Health Education and Digital Learning, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan

[n]College of Public Health, National Taiwan University, Taipei, Taiwan

[o]Graduate Institute of Sports and Health Management, National Chung Hsing University, Taichung, Taiwan

[p]Taipei Association of Health and Welfare Data Science, Taipei, Taiwan

[q]Section of Infectious Diseases, Taipei City Hospital, Yangming Branch, Taipei, Taiwan

[s]Department of Education and Research, Taipei City Hospital, Taiwan

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[#]Shang-Yih Chan, Yun-Ju Lai, and Ming-Chung Ko contributed equally to this manuscript.

Correspondence: Yung-Feng Yen

Section of Infectious Diseases, Taipei City Hospital, Taipei City Government, Taipei,

Taiwan, No.145, Zhengzhou Rd., Datong Dist., Taipei City 10341, Taiwan (Tel: +

886-2-2835-3456; e-mail: yfyen1@gmail.com)

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Strengths and limitations of this study

- This study is the first and largest cohort study to compare the utilization of hospice care services in people living with HIV (PLWH) and HIV-negative individuals during end-of-life (EOL) care.
- The research design included unbiased subject selection and strict HIV diagnostic criteria, which enhances the validity of the findings.
- This nationwide population-based study traced all PLWH and controls with referral bias being minimized because all medical care is covered by the Taiwan National Health Insurance.
- Some important factors (e.g., individuals' religion) associated with patients' decision on receiving hospice care services were not collected in this study.

Abstract:

Objective: Hospice care could improve the quality of life among advanced HIV patients during end-of-life (EOL) treatment. However, providing hospice care services for people living with HIV (PLWH) is challenging due to HIV-related stigma. This nationwide cohort study aims to determine the utilization of hospice care services among PLWH and HIV-negative individuals during EOL treatment.

Design: A retrospective cohort study.

Setting: From 2000–2018, we identified adult PLWH from the Taiwan centers for disease control HIV Surveillance System. Individuals who had positive HIV-1 western blots were regarded as HIV-infected. Age- and sex-matched controls without HIV infection were selected from the Taiwan National Health Insurance Research Database for comparison. All PLWH and controls were followed until death or December 31, 2018.

Participants: 32,647 PLWH and 326,470 HIV-negative controls were analyzed.

Primary outcome measures: Utilization of hospice care services during the last year of life among PLWH and HIV-negative individuals.

Results: A total of 20,413 subjects died during the 3,434,699 person-years of follow-up. Of the deceased patients, 2,139 (10.5%) utilized hospice care services during their last year of life, including 328 (5.76%) PLWH and 1,811 (12.30%) controls. Adjusting for demographics and comorbidities, PLWH were less likely to receive hospice care services during the last year of life, compared with HIV-negative individuals (Adjusted odds ratio: 0.66; 95% confidence interval: 0.57–0.75).

Conclusions: PLWH had a significantly lower utilization of hospice care services during the last year of life. Our results support the need to increase optimal hospice care services among PLWH during their EOL treatment.

Keywords: HIV; end-of-life; hospice care; cohort study

Introduction

Hospice care is the standard of care for patients with life-limiting diseases and is recommended for those with a finite life expectancy. Previous reports have revealed that hospice care could improve the quality of end-of-life (EOL) treatment among patients with life-limiting diseases.[1 2] However, the WHO has estimated that 40 million patients with life-limiting diseases need hospice care; yet, only 15% of these patients receive this care.[3]

The advent of highly active antiretroviral therapy (HAART) has significantly improved the survival among people living with HIV (PLWH).[4] However, many PLWH in the HAART era still progress to advanced acquired immune deficiency syndrome (AIDS).[5] Hospice care among advanced HIV patients could relieve pain and improve their quality of life during EOL treatment.[6 7] However, providing hospice care services for PLWH is challenging due to HIV-related stigma. A previous study in Uganda found that fear of stigma and concerns regarding the disclosure of their AIDS diagnosis were major barriers for PLWH when participating in hospice care.[8]

Hospice care is associated with improving PLWH's wellbeing during their EOL treatment and has been recommended for PLWH with a limited life expectancy.[7] However, studies determining the utilization of hospice care services among PLWH are limited. A retrospective cohort study involving 367 HIV patients hospitalized in a

large urban hospital in the US found that 28% of PLWH died during that hospitalization, but only 6% received a palliative care consultation, and 6% were enrolled in hospice.[9]

Hospice care programs should particularly focus on the most disadvantaged groups not benefitting from hospice care services during EOL treatment. Therefore, we conducted a nationwide population-based cohort study from 2000 to 2018 to determine the utilization of hospice care services among PLWH and HIV-negative individuals during their EOL treatment.

Methods

Data source

This cohort study used data from the Taiwan centers for disease control (CDC) HIV Surveillance Database from 2000 to 2018. In Taiwan, medical professionals must by law report all new HIV cases to the Taiwan CDC within 24 hours of diagnosis. Reported HIV-infected cases were defined as those with positive HIV-1 western blot or polymerase chain reaction analysis results. All HIV-infected individuals in Taiwan have been offered free-of-charge HAART since 1997.[10] This study was approved by the Institutional Review Board of Taipei City Hospital (no. TCHIRB-10709107-W) and all methods were performed in accordance with relevant guidelines and regulations. The informed consents for study participants were waived in this report.

Study subjects

This cohort study linked the Taiwan CDC HIV Surveillance Database to the Taiwan National Health Insurance Research Database. Adult PLWH (aged ≧18 years) were selected from the Taiwan CDC HIV Surveillance Database from 2000 through 2018.

The control group (HIV-negative individuals) was selected from the Taiwan National Health Insurance Research Database. In Taiwan, more than 99% of Taiwanese citizens are covered by the National Health Program, since 1995.[11] The

control group was matched for age, sex, and date of enrollment (±7 days). Ten controls were randomly selected for each HIV patient.[12 13] Control subjects were excluded if they had been reported to the Taiwan CDC as HIV-infected cases before inclusion in the study. All HIV patients and controls were followed until death, or up to December 31, 2018. Data on death events were obtained from the death certificate database of Taiwan.[14] We included deceased HIV-infected and HIV-negative patients in the analysis to compare the utilization of hospice care services between two groups during the last year of life.

Outcome variable

The outcome variable was the utilization of hospice care services during the last year of life among PLWH and the control group, which were determined through the patients' medical records. Hospice care services included hospice inpatient care, hospice-shared care, and hospice home care.[15]

Main explanatory variable

The main explanatory variable was HIV infection. Individuals with positive HIV-1 western blots or polymerase chain reaction analysis results were regarded as those with HIV infection.

Control variables

The control variables included sociodemographic characteristics and comorbidities

Sociodemographic factors included age, sex, income level, and urbanization. The income level was calculated from the average monthly income of the insured person and grouped into three levels: low (≤ 19,200 New Taiwan Dollars [NTD]), intermediate (19,201 NTD to < 40,000 NTD), and high (≥ 40,000 NTD). Urbanization was categorized as subjects residing in urban, suburban, or rural areas.[16] The comorbidities were defined as the presence of an appropriate International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) code, including cancer, diabetes, chronic kidney disease, congestive heart failure, coronary heart disease, liver cirrhosis, chronic obstructive pulmonary disease, dementia, and cerebrovascular disease (Supplementary table 1). A person was considered to have comorbidities only if the condition occurred in an inpatient setting or in three or more outpatient visits.[17]

Patient and Public Involvement

No patient involved in the development of the research question, study design, outcome measures and conduction of the study.

Statistical analysis

First, all subjects' demographic data were analyzed. Continuous data were presented as the mean (standard deviation [SD]), and a two-sample *t*-test was used to compare groups. Categorical data were analyzed using a Pearson's χ^2 test, where appropriate.

We assessed the crude associations of HIV infection and other covariates with the outcome (utilization of hospice care services during the last year of life) by computing the odds ratios (ORs) and corresponding 95% confidence intervals (CIs). A multivariate logistic regression was used to estimate the association between HIV infection and the utilization of hospice care services, after adjusting for potential confounders. A variable with $p < 0.05$ was defined as a significant factor associated with utilizing hospice care services in the multivariate analysis. Adjusted odds ratios (AOR) with 95% CIs were reported to indicate the strength and direction of these associations.

To examine the robustness of the main findings, subgroup and sensitivity analyses were conducted after stratifying study subjects by age and sex. All data management and analyses were performed using the SAS 9.4 statistical software package (SAS Institute, Cary, NC, USA).

Results

Subject selection

A total of 32,647 adult HIV-infected individuals were reported to the Taiwan CDC from 2000 to 2018. Another 326,470 age- and sex-matched subjects without HIV infection were randomly selected for the control group (Table 1). During the 3,434,699 person-years of follow-up, 20,413 subjects died, including 5,691 (17.43%) of the PLWH and 14,722 (4.51%) of the control group.

Characteristics of deceased patients by HIV status

Table 2 shows the characteristics of deceased patients with and without HIV infection. Compared with HIV-negative individuals, PLWH were more likely to be younger (39.3 vs. 44.7 years) and female. Moreover, PLWH had lower proportion of comorbidities than control group. During the follow-up period, 2,139 patients utilized hospice care services during their last year of life, including 328 (5.76%) PLWH and 1,811 (12.30%) HIV-negative individuals.

Factors associated with utilization of hospice care services during the last year of life

Table 3 shows the univariate and multivariate analyses of factors associated with the utilization of hospice care services during the last year of life among deceased patients. After adjusting for the sociodemographic factors and co-morbidities, HIV

infection was significantly associated with lower utilization of hospice care services during the last year of life (AOR: 0.66; 95% CI: 0.57–0.75; Table 2). Other factors associated with a lower utilization of hospice care service were age ≥65 years and men. Factors associated with higher utilization of hospice care services included intermediate and high income levels and the comorbidities of cancer and COPD.

Sensitivity analysis of the association between HIV infection and utilization of hospice care services

Table 4 shows the results of sensitivity analysis of the association between HIV infection and utilization of hospice care services after stratifying study subjects by age and sex. HIV infection was associated with a lower utilization of hospice care services during the last year of life among male subjects and those aged 15–64.

Discussion

The present study is the first longitudinal study on the utilization of hospice care services among PLWH and HIV-negative individuals during their EOL treatment. The results indicate that PLWH had a significantly lower utilization of hospice care services during EOL treatment compared with age- and sex-matched HIV-negative individuals.

Our study showed robust associations between HIV infection and utilization of hospice care services after stratifying subjects by age and sex. HIV infection is associated with a lower likelihood of receiving hospice care services among male subjects and those aged 15–64 years.

Hospice care could improve PLWH's quality of life during their EOL treatment.[7] However, there are limited studies evaluating the utilization of hospice care services among PLWH. A retrospective cohort study including 367 HIV patients hospitalized in a large urban safety-net hospital showed that 28% of the patients died during such hospitalization. However, only 6% of the patients were enrolled in hospice.[9] Our study followed up 32,647 HIV patients and found that 5.76% of PLWH received hospice care services during their EOL treatment. While comparing with HIV-negative individuals, PLWH had a significantly lower utilization of hospice care services during the last year of life. The findings of our study suggest that hospice

care is underutilized among PLWH and it is imperative to increase optimal hospice care services among PLWH during EOL treatment.

This study showed that PLWH had a 34% lower likelihood of receiving hospice care services during EOL treatment as compared to HIV-negative individuals. HIV-related stigma and professionals' lack of experience in treating advanced HIV may explain for the lower utilization of hospice care services in PLWH toward the end of life. HIV-related stigma remains prevalent in society,[18] which would cause the PLWH's unwillingness to disclose their HIV status. Since the process of participating in hospice care services involves a discussion regarding EOL treatment's preferences among PLWH, patients' family, and healthcare providers,[19] HIV-related stigma and PLWH's disclosure concern of their HIV status would lead to the lower likelihood of them agreeing with having an EOL discussion with physicians. A qualitative study in Uganda showed that HIV patients' fear of such a stigma and their concern regarding the disclosure of their AIDS diagnosis were the major hurdles when participating in hospice care.[8] Since hospice care is associated with the relief of pain and improving the quality of care among patients nearing death,[6 7] it is important to provide hospice care services for PLWH during EOL treatment.

Professionals' lack of experience in treating advanced HIV patients needing palliative care may also explain for the lower utilization of hospice care services

among PLWH toward the end of life. The provision of hospice care services among PLWH is complex, which looks into whether the patients should continue treatment with antiretroviral drugs and whether the patients should request the concealment of their HIV status from their families. Although there are no guidelines in informing clinicians on when to stop HAART among advanced HIV patients enrolling in hospice care, the side effects and pill burden of antiretroviral drugs may decrease the PLWH's quality of life during EOL treatment.[20] The decision to discontinue antiretroviral therapy for advanced HIV patients receiving hospice care should be considered through a comprehensive discussion with patients and their families. Healthcare providers may be not familiar with these issues regarding the timing to discontinue HAART and concealment of HIV infection from their families among PLWH needing hospice care. As such, this would cause the professionals' lower likelihood of providing hospice care services for advanced HIV patients. A previous nationwide hospital survey in Japan showed that 11.2% of healthcare providers at palliative care units were not willing to provide EOL care for PLWH due to lack of knowledge and experience in treating advanced HIV patients nearing death.[21] Since hospice and palliative care services are associated with improvements in quality of life among patients toward the end of life,[7] it is important to provide hospice care service for PLWH during EOL treatment.

This nationwide cohort study has several strengths. First, this study is the first and largest cohort study to compare the utilization of hospice care services in PLWH and HIV-negative individuals during EOL care. Our research design included unbiased subject selection and strict HIV diagnostic criteria, which enhances the validity of the findings. Additionally, this nationwide population-based study traced all PLWH and controls with referral bias being minimized because all medical care is covered by the Taiwan National Health Insurance. Furthermore, our large sample size was sufficiently powered to detect the real—albeit subtle—difference between PLWH and controls.

The study nevertheless has two limitations. First, there may be important factors (e.g., individuals' religion) associated with their decision on receiving hospice care services that were not recorded in the National Health Insurance Research Database. Second, the external validity of our findings may be a concern, as almost all our subjects were Taiwanese. The generalizability of our results to other non-Asian ethnic groups requires further verification. However, our findings suggest new avenues for future research.

Conclusion

This nationwide cohort study found that only 5.76% of PLWH received hospice care services during EOL treatment. Compared with HIV-negative individuals, PLWH had a significantly lower utilization of hospice care services during EOL treatment. As hospice care service could relieve pain and improve patients' spiritual wellbeing during EOL care, future hospice care programs should particularly target PLWH to increase the optimal utilization of hospice care services during EOL treatment.

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Authors' contributions

SYC, YJL, MCK, YYC, YFT, LFH, PWK, LJC, PHC, CCC, and YFY substantially contributed to the conception and design of the study, data analysis, data interpretation, and the drafting of the manuscript. SYC, YJL, MCK, YYC, YFT, LFH, PWK, LJC, PHC, and YFY substantially contributed to data acquisition and interpretation of the results. SYC, YJL, MCK, YYC, YFT, LFH, PWK, LJC, PHC, CCC, and YFY all approved the final version of the manuscript.

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Competing interests

All authors: No reported conflicts.

Data sharing statement

Data analysis was guided by the monitoring regulation guidelines of Scientific Data Center of the Minister of Health and Welfare, Taiwan. All the data is open for accessing following the approved security protocols with specific processes.

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Table 1 People living with HIV and matched controls

Characteristics	No. (%) of subjects*		p-value
	Patients with HIV, n = 32,647	Patients without HIV, n = 326,470	
Demographics			
Age, yrs			
Mean ± SD	32.68 ± 10.12	32.68 ± 10.12	1
18-64	32252 (98.79)	322520 (98.79)	1
≥65	395 (1.21)	3950 (1.21)	
Sex			
Female	1913 (5.86)	19130 (5.86)	1
Male	30734 (94.14)	307340 (94.14)	
Death			
No	26956 (82.57)	311748 (95.49)	<.001
Yes	5691 (17.43)	14722 (4.51)	
Total follow-up duration (person-years)	283,112	3,151,587	<.001

HIV, human immunodeficiency virus; SD, standard deviation; *Unless stated otherwise.

Table 2 Characteristics of deceased patients by HIV status

Characteristics	No. (%) of subjects*		P value
	Deceased patients with HIV, n = 5,691	Deceased patients without HIV, n = 14,722	
Demographics			
Age, yrs			
Mean ± SD	39.27 ± 12.74	44.73 ± 15.30	<.001
18-64	5,410 (95.06)	12,765 (86.71)	<.001
≥65	281 (4.94)	1,957 (13.29)	
Sex			<.001
Female	433 (7.61)	633 (4.30)	
Male	5,258 (92.39)	14,089 (95.70)	
Income level			<.001
Low	2,112 (37.11)	4,540 (30.84)	
Intermediate	2,619 (46.02)	6,740 (45.78)	
High	960 (16.87)	3,442 (23.38)	
Urbanization			<.001
Rural	491 (8.63)	1,601 (10.87)	
Suburban	3,228 (56.72)	9,289 (63.10)	
Urban	1,972 (34.65)	3,832 (26.03)	
Comorbidity			
Cancer	1,149 (20.19)	5,076 (34.48)	<.001
Diabetes	881 (15.48)	3,857 (26.20)	<.001
Chronic kidney disease	754 (13.25)	2,814 (19.11)	<.001
Congestive heart failure	381 (6.69)	1,822 (12.38)	<.001
Coronary heart disease	691 (12.14)	3,132 (21.27)	<.001
Liver cirrhosis	751 (13.20)	2,652 (18.01)	<.001
COPD	1,212 (21.30)	3,546 (24.09)	<.001
Dementia	65 (1.14)	546 (3.71)	<.001
Cerebrovascular disease	678 (11.91)	3,114 (21.15)	<.001
Utilization of hospice care services during the last year of life	328 (5.76)	1,811 (12.30)	<.001

HIV, human immunodeficiency virus; SD, standard deviation; COPD, chronic obstructive pulmonary disease. *Unless stated otherwise.

Table 3 Univariate and multivariate analysis of factors associated with utilization of hospice care services during the last year of life among deceased patients

Variables	Number of patients	Utilization of hospice care services[a]	Univariate	Multivariate analysis
		n (%)	OR (95%CI)	AOR (95%CI)
HIV infection				
No	14,722	1811 (12.30)	1	1
Yes	5,691	328 (5.76)	0.44 (0.39-0.49)***	0.66 (0.57-0.75)***
Demographics				
Age, yrs				
18-64	18,175	1921 (10.57)	1	1
≥65	2,238	218 (9.74)	0.91 (0.79-1.06)	0.59 (0.49-0.70)***
Sex				
Female	1,066	150 (14.07)	1	1
Male	19,347	1989 (10.28)	0.70 (0.59-0.84)***	0.66 (0.54-0.81)***
Income level				
Low	6,652	359 (5.40)	1	1
Intermediate	9,359	1086 (11.60)	2.30 (2.03-2.60)***	1.96 (1.72-2.25)***
High	4,402	694 (15.77)	3.28 (2.87-3.75)***	2.21 (1.90-2.57)***
Urbanization				

Rural	2,092	209 (9.99)	1	1
Suburban	12,517	1305 (10.43)	1.05 (0.90-1.22)	0.97 (0.82-1.16)
Urban	5,804	625 (10.77)	1.09 (0.92-1.28)	0.95 (0.79-1.15)
Comorbidity				
Cancer				
No	14188	234 (1.65)	1	1
Yes	6225	1905 (30.60)	26.30 (22.86-30.25)***	24.48 (21.23-28.24)***
Diabetes				
No	15675	1588 (10.13)	1	1
Yes	4738	551 (11.63)	1.17 (1.05-1.29)**	1.05 (0.93-1.19)
Chronic kidney disease				
No	16845	1738 (10.32)	1	1
Yes	3568	401 (11.24)	1.10 (0.98-1.24)	0.97 (0.84-1.11)
Congestive heart failure				
No	18210	1947 (10.69)	1	1
Yes	2203	192 (8.72)	0.80 (0.68-0.93)**	0.99 (0.81-1.20)
Coronary heart disease				
No	16590	1701 (10.25)	1	1
Yes	3823	438 (11.46)	1.13 (1.01-1.27)*	1.02 (0.89-1.18)
Liver cirrhosis				
No	17010	1648 (9.69)	1	1
Yes	3403	491 (14.43)	1.57 (1.41-1.75)***	0.97 (0.86-1.10)

COPD				
No	15655	1533 (9.79)	1	1
Yes	4758	606 (12.74)	1.35 (1.22-1.49)***	1.15 (1.02-1.29)*
Dementia				
No	19802	2090 (10.55)	1	1
Yes	611	49 (8.02)	0.74 (0.55-0.99)*	0.92 (0.65-1.30)
Cerebrovascular disease				
No	16621	1810 (10.89)	1	1
Yes	3792	329 (8.68)	0.78 (0.69-0.88)***	0.87 (0.75-1.00)

*<.05; **<.01; ***<.001.

[a]during the last year of life.

AOR, adjusted odds ratio; CI, confident interval; COPD, chronic obstructive pulmonary disease.

Table 4 Sensitivity analysis for the associations between HIV infection and utilization of hospice care services after adjusting for patient characteristics

Study subgroups	Utilization of hospice care services	
	AOR (95% CI)[a]	P value
All patients (n=20413)	0.66 (0.57-0.75)	<.001
Aged 15–64 (n=18175)	0.66 (0.57-0.76)	<.001
Aged ≥ 65 (n=2238)	0.74 (0.43-1.26)	0.271
Male patients (n=19347)	0.66 (0.57-0.76)	<.001
Female patients (n=1066)	0.80 (0.48-1.31)	0.372

HIV, human immunodeficiency virus; AOR, adjusted odds ratio; CI, confident interval.

[a]during the last year of life.

Supplementary table 1 ICD-9-CM and ICD-10-CM codes for comorbidities

Comorbidities	ICD-9-CM code	ICD-10-CM code
Cancer	140~208	C, D0
Diabetes	250	E08~E13
Chronic kidney disease	585, 586	N18
Congestive heart failure	428, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93	I50, I0981, I110, I130, I132
Coronary heart disease	410~414	I20~I25
Liver cirrhosis	571, 571.2, 571.5, 571.6	K703, K717, K746
Chronic obstructive pulmonary disease	491, 492, 518.1, 518.2, 770.2	J41~J44
Dementia	290	F01~F03
Cerebrovascular disease	430~437	G46.3, G46.4, I60~I66, I69
Opportunistic infections		
Cytomegalovirus disease	(078.5	B25
Tuberculosis	010~018	A15~A19
Disseminated Mycobacterium avium complex infection	31.2	A31.2

Pneumocystis jirovecii pneumonia (or pneumocystis carinni pneumonia)	136.3	B59
Cryptococcal meningitis	(321.0	B45.1
Candidiasis	112	B37
Penicillium marneffei infection	117.9	B48.3, B48.8, B49
Herpes zoster	((053)	B02
AIDS-related cancer		
Kaposi sarcoma	176	C46
Non-Hodgkin lymphoma	202.8	C85.8, C85.9
Cervix	180	C53.9

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; AIDS, acquired immune deficiency syndrome.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	11
		(*e*) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-13 12 12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Is there lower utilization of hospice care services during end-of-life care for people living with HIV? A population-based cohort study

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Complete List of Authors:	Chan, Shang-Yih; Taipei City Hospital Yangming Branch, Department of Internal Medicine; National Taipei University of Nursing and Health Sciences, Department of Health Care Management Lai, Yun-Ju; National Taipei University of Nursing and Health Sciences, Department of Health Care Management; Puli Branch of Taichung Veterans General Hospital, Department of Internal Medicine Ko, Ming-Chung ; Taipei City Hospital, Department of Urology; National Taipei University of Nursing and Health Sciences, Department of Health Care Management Chen, Yu-Yen ; Taichung Veterans General Hospital; Chung Shan Medical University Tsai, Yi-Fan; Yangming Branch, Department of Nursing; Taipei Medical University Hsu, Li-Fei; National Taiwan University Ku, Po-Wen; National Chung Hsing University, Graduate Institute of Sports and Health Chen, Li-Jung; National Taiwan University of Sport, Department of Exercise Health Science Chuang, Pei-Hung ; Taipei Association of Health and Welfare Data Science Chen, Chu-Chieh ; National Taipei University of Nursing and Health Sciences Yen, Yung-Feng; Taipei City Hospital Yangming Branch; National Yang Ming Chiao Tung University, Institute of Public Health
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Is there lower utilization of hospice care services during end-of-life care for people living with HIV? A population-based cohort study

Shang-Yih Chan[a,b,c,#], Yun-Ju Lai[b,d,e,f,#], Ming-Chung Ko[b,g,#], Yu-Yen Chen[d,h,i,j], Yi-Fan Tsai[k,l,m], Li-Fei Hsu[n], Po-Wen Ku[o], Li-Jung Chen[f], Pei-Hung Chuang[p], Chu-Chieh Chen[b], Yung-Feng Yen[b,c,h,q,s*]

[a]Department of Internal Medicine, Taipei City Hospital, Yangming Branch, Taipei, Taiwan

[b]Department of Health Care Management, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan

[c]University of Taipei, Taipei, Taiwan

[d]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

[e]Division of Endocrinology and Metabolism, Department of Internal Medicine, Puli Branch of Taichung Veterans General Hospital, Nantou, Taiwan

[f]Department of Exercise Health Science, National Taiwan University of Sport, Taichung, Taiwan

[g]Department of Urology, Taipei City Hospital, Taipei, Taiwan

[h]Institute of Public Health, National Yang Ming Chiao Tung University, Taipei,

Taiwan

[i]Department of Ophthalmology, Taichung Veterans General Hospital, Taichung, Taiwan

[j]School of Medicine, Chung Shan Medical University, Taichung, Taiwan

[k]Department of Nursing, Taipei City Hospital, Yangming Branch, Taipei, Taiwan

[l]School of Nursing, Taipei Medical University, Taipei, Taiwan

[m]Department of Allied Health Education and Digital Learning, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan

[n]College of Public Health, National Taiwan University, Taipei, Taiwan

[o]Graduate Institute of Sports and Health Management, National Chung Hsing University, Taichung, Taiwan

[p]Taipei Association of Health and Welfare Data Science, Taipei, Taiwan

[q]Section of Infectious Diseases, Taipei City Hospital, Yangming Branch, Taipei, Taiwan

[s]Department of Education and Research, Taipei City Hospital, Taiwan

Running head: HIV infection and Hospice Care Services

[#]Shang-Yih Chan, Yun-Ju Lai, and Ming-Chung Ko contributed equally to this manuscript.

Correspondence: Yung-Feng Yen

Section of Infectious Diseases, Taipei City Hospital, Taipei City Government, Taipei,

Taiwan, No.145, Zhengzhou Rd., Datong Dist., Taipei City 10341, Taiwan (Tel: +886-2-2835-3456; e-mail: yfyen1@gmail.com)

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Abstract:

Objective: Hospice care could improve the quality of life among advanced HIV patients during end-of-life (EOL) treatment. However, providing hospice care services for people living with HIV (PLWH) is challenging due to HIV-related stigma. This nationwide cohort study aims to determine the utilization of hospice care services among PLWH and HIV-negative individuals during EOL treatment.

Design: A retrospective cohort study.

Setting: From 2000–2018, we identified adult PLWH from the Taiwan centers for disease control HIV Surveillance System. Individuals who had positive HIV-1 western blots were regarded as HIV-infected. Age- and sex-matched controls without HIV infection were selected from the Taiwan National Health Insurance Research Database for comparison. All PLWH and controls were followed until death or December 31, 2018.

Participants: 32,647 PLWH and 326,470 HIV-negative controls were analyzed.

Primary outcome measures: Utilization of hospice care services during the last year of life among PLWH and HIV-negative individuals.

Results: A total of 20,413 subjects died during the 3,434,699 person-years of follow-up. Of the deceased patients, 2,139 (10.5%) utilized hospice care services during their last year of life, including 328 (5.76%) PLWH and 1,811 (12.30%) controls. Adjusting for demographics and comorbidities, PLWH were less likely to receive hospice care services during the last year of life, compared with HIV-negative individuals (Adjusted odds ratio: 0.66; 95% confidence interval: 0.57–0.75).

Conclusions: PLWH had significantly lower utilization of hospice care services during the last year of life. Our results suggest that future hospice care programs should particularly target PLWH to increase the optimal utilization of hospice care services during EOL treatment.

Keywords: HIV; end-of-life; hospice care; cohort study

Strengths and limitations of this study

- This study used the Taiwan CDC HIV Surveillance Database to determine the utilization of hospice care services among people living with HIV during end-of-life treatment.
- HIV-infected cases were defined as those with positive HIV-1 western blot.
- Age- and sex-matched controls without HIV infection were selected from the Taiwan National Health Insurance Research Database for comparison.
- Individuals' religion, which may be associated with their decision on receiving hospice care services, was not collected in the National Health Insurance Research Database.

Introduction

Hospice care has been recommended for patients with life-limiting diseases. Previous studies showed that hospice care was associated with good quality of end-of-life (EOL) treatment among patients with life-limiting diseases.[1 2] The World Health Organization (WHO) estimated that 40 million patients with life-limiting diseases need palliative care.[3] However, over 85% of these patients do not receive this care during their EOL treatment.[3]

The advent of highly active antiretroviral therapy (HAART) has significantly improved the survival among people living with HIV (PLWH).[4] However, many PLWH in the HAART era still progress to advanced acquired immune deficiency syndrome (AIDS).[5] Hospice care among advanced HIV patients could relieve pain and improve their quality of life during EOL treatment.[6 7] However, providing hospice care services for PLWH is challenging due to HIV-related stigma. A previous survey about attitudes toward hospice care among PLWH reported that hospice services were perceived to provide essential relief from pain and symptoms during the EOL treatment.[8] However, fear of stigma and concerns regarding the disclosure of their AIDS diagnosis were major barriers for PLWH when participating in hospice care.[8]

Hospice care is associated with improving PLWH's wellbeing during their EOL treatment and has been recommended for PLWH with a limited life expectancy.[7]

However, studies determining the utilization of hospice care services among PLWH are limited. A retrospective cohort study involving 367 HIV patients hospitalized in a large urban hospital in the US found that 28% of PLWH died during that hospitalization, but only 6% received a palliative care consultation, and 6% were enrolled in hospice.[9] Another retrospective study using the US Medicare database showed that 24.6% of terminal patients with HIV received hospice care during EOL treatment.[10]

Understanding the utilization of hospice care services in PLWH during EOL treatment could guide the comprehensive HIV care program. Therefore, this nationwide population-based cohort study aims to determine the utilization of hospice care services among PLWH and HIV-negative individuals during their EOL treatment from 2000 to 2018.

Methods

Data source and study patients

This population-based cohort study identified adult PLWH from the Taiwan Centers for Disease Control (CDC) HIV Surveillance System between 2000 and 2018. In Taiwan, hospital institutes are required to report all new HIV cases to the Taiwan CDC within 24 hours of diagnosis. Individuals who had positive HIV-1 western blots or polymerase chain reaction analysis results were regarded as HIV-infected. In Taiwan, HAART has been offered free-of-charge to all HIV-infected individuals since 1997.[11]

This cohort study linked the Taiwan National Health Insurance Research Database to the Taiwan CDC HIV Surveillance Database. The control group was selected from the Taiwan National Health Insurance Research Database and included those who had never been reported to the Taiwan CDC as HIV-infected cases. The control group was matched for age, sex, and date of enrollment (±7 days). Ten controls were randomly selected for each HIV patient.[12 13] All HIV patients and controls were followed until death or up to December 31, 2018. The death events among HIV patients and controls were verified using the death certificate database of Taiwan.[14] To compare the utilization of hospice care services between patients who were HIV-infected and HIV-negative during their last year of life, this study only included deceased PLWH

and controls in the analysis.

This study was approved by the Institutional Review Board of Taipei City Hospital (no. TCHIRB-10709107-W). All methods in this study were performed in accordance with relevant guidelines and regulations, and the informed consents for study patients were waived in this report.

Outcome variable

The outcome was the utilization of hospice care services during the last year of life among PLWH and the control group. This study used the Taiwan National Health Insurance Research Database to determine the utilization of hospice care services during the last year of life between the two groups. Hospice care services consisted of hospice inpatient care, hospice home care, and hospice-shared care.[15]

Main explanatory variable

The main explanatory variable was HIV infection. HIV-infected individuals were defined as those with positive HIV-1 western blot or polymerase chain reaction analysis results.

Control variables

The control variables included sociodemographic characteristics and comorbidities Sociodemographic factors included age, sex, income level, and urbanization. The income level in study patients was calculated from their average monthly income and grouped into three levels: (1) low-income level, defined as an amount lower than the US $640 per month, (New Taiwan Dollars (NTD) $19,200); (2) moderate-income level, defined as an amount between the US $1332 and 640 per month, (<40 000 NTD to 19 201); and (3) high-income level, defined as an amount more than the US $1333 per month, (40 000 NTD). Urbanization was classified as urban, suburban, or rural areas.[16] The comorbidities were defined as the presence of an appropriate International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) code, including cancer, diabetes, chronic kidney disease, congestive heart failure, coronary heart disease, liver cirrhosis, chronic obstructive pulmonary disease, dementia, and cerebrovascular disease (Supplementary table 1). The comorbidities in study patients were defined as the condition occurred in an inpatient setting or in three or more outpatient visits.[17]

Patient and Public Involvement

No patient involved in the development of the research question, study design,

outcome measures and conduction of the study.

Statistical analysis

Continuous data in study patients were presented as the mean (standard deviation [SD]), and a two-sample *t*-test was used to compare groups. We then analyzed categorical data using the Pearson χ^2 test wherever appropriate.

The crude associations of HIV infection and other covariates with the outcome (utilization of hospice care services during the last year of life) were estimated by computing the odds ratios (ORs) and corresponding 95% confidence intervals (CIs). We then performed a multivariate logistic regression to assess the association between HIV infection and the utilization of hospice care services, after adjusting for the sociodemographic factors and co-morbidities. Thus, we defined a variable with $p<0.05$ as a significant factor affecting this association. Adjusted odds ratios (AOR) with 95% confidence intervals (CI) indicated the strength and direction of these associations.

We conducted subgroup and sensitivity analyses to examine the robustness of the main findings after stratifying patients by age and sex. We performed all data management and analyses using the SAS® v9.4 statistical software package (SAS Institute, Cary, NC, USA).

Results

Patient selection

A total of 32,647 adult HIV-infected individuals were reported to the Taiwan CDC from 2000 to 2018. Another 326,470 age- and sex-matched patients without HIV infection were randomly selected for the control group (Table 1). During the 3,434,699 person-years of follow-up, 20,413 patients died, including 5,691 (17.43%) of the PLWH and 14,722 (4.51%) of the control group.

Characteristics of deceased patients by HIV status

Table 2 shows the characteristics of deceased patients with and without HIV infection. In comparison to with HIV-negative individuals, PLWH were more likely to be younger (39.3 vs. 44.7 years) and female. Moreover, PLWH had lower proportion of comorbidities than control group. During the study follow-up period, 2,139 patients utilized hospice care services during their last year of life, including 328 (5.76%) PLWH and 1,811 (12.30%) HIV-negative individuals.

Factors associated with utilization of hospice care services during the end-of-life treatment in deceased patients

Table 3 shows the univariate and multivariate analyses of factors associated with the utilization of hospice care services during the last year of life among deceased patients. After adjusting for the potential confounders, HIV infection was significantly

associated with lower utilization of hospice care services during the last year of life (AOR: 0.66; 95% CI: 0.57–0.75; Table 2). Moreover, age ≥65 years and men were associated with a lower utilization of hospice care service during the last year of life. Factors associated with higher utilization of hospice care services included intermediate and high-income levels and the comorbidities of cancer and COPD.

Subgroup analysis for the association between HIV infection and utilization of hospice care services

Table 4 shows the results of subgroup analysis for the association between HIV infection and utilization of hospice care services after stratifying study patients by age and sex. HIV infection was associated with a lower utilization of hospice care services during the last year of life among male patients and those aged 15–64.

Discussion

The present study is the largest cohort study on the utilization of hospice care services among PLWH and HIV-negative individuals during their EOL treatment. The results indicate that PLWH had a significantly lower utilization of hospice care services during EOL treatment compared with age- and sex-matched HIV-negative individuals.

Our study showed robust associations between HIV infection and utilization of hospice care services after stratifying patients by age and sex. HIV infection is associated with a lower likelihood of receiving hospice care services among male patients and those aged 15–64 years.

Hospice care could improve PLWH's quality of life during their EOL treatment.[7] However, there are limited studies evaluating the utilization of hospice care services among PLWH. A retrospective cohort study including 367 HIV patients hospitalized in a large urban safety-net hospital showed that 28% of the patients died during such hospitalization. However, only 6% of the patients were enrolled in hospice.[9] Another retrospective study involving 1,375 HIV patients in the US found that 24.6% of terminal Medicare patients with HIV received hospice care during EOL treatment.[10] Our study followed up 32,647 HIV patients and found that 5.76% of PLWH received hospice care services during their EOL treatment. While comparing with

HIV-negative individuals, PLWH had a significantly lower utilization of hospice care services during the last year of life. The findings of our study suggest that hospice care is underutilized among PLWH and it is imperative to increase optimal hospice care services among PLWH during EOL treatment.

This study showed that PLWH had a 34% lower likelihood of receiving hospice care services during EOL treatment as compared to HIV-negative individuals. HIV-related stigma and professionals' lack of experience in treating advanced HIV may explain for the lower utilization of hospice care services in PLWH toward the end of life. HIV-related stigma remains prevalent in society,[18] which would cause the PLWH's unwillingness to disclose their HIV status. Since the process of participating in hospice care services involves a discussion regarding EOL treatment's preferences among PLWH, patients' family, and healthcare providers,[19] HIV-related stigma and PLWH's disclosure concern of their HIV status would lead to the lower likelihood of them agreeing with having an EOL discussion with physicians. A qualitative study in Uganda showed that HIV patients' fear of such a stigma and their concern regarding the disclosure of their AIDS diagnosis were the major hurdles when participating in hospice care.[8] Since hospice care is associated with the relief of pain and good quality of care among patients nearing death,[6 7] it is imperative to provide hospice care services for PLWH during EOL treatment.

Professionals' lack of experience in treating advanced HIV patients needing palliative care may also explain for the lower utilization of hospice care services among PLWH toward the end of life. The provision of hospice care services among PLWH is complex, which looks into whether the patients should continue treatment with antiretroviral drugs and whether the patients should request the concealment of their HIV status from their families. Although there are no guidelines in informing clinicians on when to stop HAART among advanced HIV patients enrolling in hospice care, the side effects and pill burden of antiretroviral drugs may decrease the PLWH's quality of life during EOL treatment.[20] The decision to discontinue antiretroviral therapy for advanced HIV patients receiving hospice care should be considered through a comprehensive discussion with patients and their families. Healthcare providers may be not familiar with these issues regarding the timing to discontinue HAART and concealment of HIV infection from their families among PLWH needing hospice care. As such, this would cause the professionals' lower likelihood of providing hospice care services for advanced HIV patients. A previous nationwide hospital survey in Japan showed that 11.2% of healthcare providers at palliative care units were not willing to provide EOL care for PLWH due to lack of knowledge and experience in treating advanced HIV patients nearing death.[21] Since hospice and palliative care services are associated with improvements in quality of

life among patients toward the end of life,[7] it is important to provide hospice care service for PLWH during EOL treatment.

This nationwide cohort study has several strengths. First, this study is the largest cohort study to compare the utilization of hospice care services in PLWH and HIV-negative individuals during EOL care. Our research design included strict HIV diagnostic criteria, which improves the validity of the main findings. Moreover, this nationwide cohort study followed up all PLWH and controls with referral bias being minimized because all medical care is covered by the Taiwan National Health Insurance. Furthermore, the study's large sample size was sufficiently powered to detect the real, even subtle, difference between PLWH and controls.

The study nevertheless has two limitations. First, individuals' religion that may be associated with their decision on receiving hospice care services was not collected in the National Health Insurance Research Database. Second, since almost all our patients were Taiwanese, the external validity of our findings may be a concern. Therefore, future studies are needed to verify our results in other non-Asian ethnic groups.

Conclusion

This population-based cohort study showed that only 5.76% of PLWH received hospice care services during EOL treatment. Compared with HIV-negative individuals, PLWH had a significantly lower utilization of hospice care services during EOL treatment. As hospice care service could relieve pain and improve patients' spiritual wellbeing during EOL care, future hospice care programs should particularly target PLWH to increase the optimal utilization of hospice care services during EOL treatment.

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Authors' contributions

SYC, YJL, MCK, YYC, YFT, LFH, PWK, LJC, PHC, CCC, and YFY substantially contributed to the conception and design of the study, data analysis, data interpretation, and the drafting of the manuscript. SYC, YJL, MCK, YYC, YFT, LFH, PWK, LJC, PHC, and YFY substantially contributed to data acquisition and interpretation of the results. SYC, YJL, MCK, YYC, YFT, LFH, PWK, LJC, PHC, CCC, and YFY all approved the final version of the manuscript.

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Competing interests

All authors: No reported conflicts.

Data sharing statement

Data analysis was guided by the monitoring regulation guidelines of Scientific Data Center of the Minister of Health and Welfare, Taiwan. All the data is open for accessing following the approved security protocols with specific processes.

Ethical Approval Statement

This study was approved by the Institutional Review Board of Taipei City Hospital (no. TCHIRB-10709107-W) and all methods were performed in accordance with relevant guidelines and regulations. The informed consents for study participants were waived in this report.

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Table 1 People living with HIV and matched controls

Characteristics	No. (%) of patients*		p-value
	Patients with HIV, n = 32,647	Patients without HIV, n = 326,470	
Demographics			
Age, yrs			
Mean ± SD	32.68 ± 10.12	32.68 ± 10.12	1
18-64	32252 (98.79)	322520 (98.79)	1
≥65	395 (1.21)	3950 (1.21)	
Sex			
Female	1913 (5.86)	19130 (5.86)	1
Male	30734 (94.14)	307340 (94.14)	
Death			
No	26956 (82.57)	311748 (95.49)	<.001
Yes	5691 (17.43)	14722 (4.51)	
Total follow-up duration (person-years)	283,112	3,151,587	<.001

HIV, human immunodeficiency virus; SD, standard deviation; *Unless stated otherwise.

Table 2 Characteristics of deceased patients by HIV status

Characteristics	No. (%) of subjects*		P value
	Deceased patients with HIV, n = 5,691	Deceased patients without HIV, n = 14,722	
Demographics			
Age, yrs			
Mean ± SD	39.27 ± 12.74	44.73 ± 15.30	<.001
18-64	5,410 (95.06)	12,765 (86.71)	<.001
≥65	281 (4.94)	1,957 (13.29)	
Sex			<.001
Female	433 (7.61)	633 (4.30)	
Male	5,258 (92.39)	14,089 (95.70)	
Income level			<.001
Low	2,112 (37.11)	4,540 (30.84)	
Intermediate	2,619 (46.02)	6,740 (45.78)	
High	960 (16.87)	3,442 (23.38)	
Urbanization			<.001
Rural	491 (8.63)	1,601 (10.87)	
Suburban	3,228 (56.72)	9,289 (63.10)	
Urban	1,972 (34.65)	3,832 (26.03)	
Comorbidity			
Cancer	1,149 (20.19)	5,076 (34.48)	<.001
Diabetes	881 (15.48)	3,857 (26.20)	<.001
Chronic kidney disease	754 (13.25)	2,814 (19.11)	<.001
Congestive heart failure	381 (6.69)	1,822 (12.38)	<.001
Coronary heart disease	691 (12.14)	3,132 (21.27)	<.001
Liver cirrhosis	751 (13.20)	2,652 (18.01)	<.001
COPD	1,212 (21.30)	3,546 (24.09)	<.001
Dementia	65 (1.14)	546 (3.71)	<.001
Cerebrovascular disease	678 (11.91)	3,114 (21.15)	<.001
Utilization of hospice care services during the last year of life	328 (5.76)	1,811 (12.30)	<.001

HIV, human immunodeficiency virus; SD, standard deviation; COPD, chronic obstructive pulmonary disease. *Unless stated otherwise.

Table 3 Univariate and multivariate analysis of factors associated with utilization of hospice care services during the last year of life among deceased patients

Variables	Number of patients	Utilization of hospice care services[a] n (%)	Univariate OR (95%CI)	Multivariate analysis AOR (95%CI)
HIV infection				
No	14,722	1811 (12.30)	1	1
Yes	5,691	328 (5.76)	0.44 (0.39-0.49)***	0.66 (0.57-0.75)***
Demographics				
Age, yrs				
18-64	18,175	1921 (10.57)	1	1
≥65	2,238	218 (9.74)	0.91 (0.79-1.06)	0.59 (0.49-0.70)***
Sex				
Female	1,066	150 (14.07)	1	1
Male	19,347	1989 (10.28)	0.70 (0.59-0.84)***	0.66 (0.54-0.81)***
Income level				
Low	6,652	359 (5.40)	1	1
Intermediate	9,359	1086 (11.60)	2.30 (2.03-2.60)***	1.96 (1.72-2.25)***
High	4,402	694 (15.77)	3.28 (2.87-3.75)***	2.21 (1.90-2.57)***
Urbanization				

Rural	2,092	209 (9.99)	1	1
Suburban	12,517	1305 (10.43)	1.05 (0.90-1.22)	0.97 (0.82-1.16)
Urban	5,804	625 (10.77)	1.09 (0.92-1.28)	0.95 (0.79-1.15)
Comorbidity				
Cancer	6225	1905 (30.60)	26.30 (22.86-30.25)***	24.48 (21.23-28.24)***
Diabetes	4738	551 (11.63)	1.17 (1.05-1.29)**	1.05 (0.93-1.19)
Chronic kidney disease	3568	401 (11.24)	1.10 (0.98-1.24)	0.97 (0.84-1.11)
Congestive heart failure	2203	192 (8.72)	0.80 (0.68-0.93)**	0.99 (0.81-1.20)
Coronary heart disease	3823	438 (11.46)	1.13 (1.01-1.27)*	1.02 (0.89-1.18)
Liver cirrhosis	3403	491 (14.43)	1.57 (1.41-1.75)***	0.97 (0.86-1.10)
COPD	4758	606 (12.74)	1.35 (1.22-1.49)***	1.15 (1.02-1.29)*
Dementia	611	49 (8.02)	0.74 (0.55-0.99)*	0.92 (0.65-1.30)
Cerebrovascular disease	3792	329 (8.68)	0.78 (0.69-0.88)***	0.87 (0.75-1.00)

*<.05; **<.01; ***<.001.

[a]during the last year of life.

AOR, adjusted odds ratio; CI, confident interval; COPD, chronic obstructive pulmonary disease.

Table 4 Sensitivity analysis for the associations between HIV infection and utilization of hospice care services after adjusting for patient characteristics

Study subgroups	Utilization of hospice care services	
	AOR (95% CI)[a]	P value
All patients (n=20413)	0.66 (0.57-0.75)	<.001
Aged 15–64 (n=18175)	0.66 (0.57-0.76)	<.001
Aged ≥ 65 (n=2238)	0.74 (0.43-1.26)	0.271
Male patients (n=19347)	0.66 (0.57-0.76)	<.001
Female patients (n=1066)	0.80 (0.48-1.31)	0.372

HIV, human immunodeficiency virus; AOR, adjusted odds ratio; CI, confident interval.

[a]during the last year of life.

Supplementary table 1 ICD-9-CM and ICD-10-CM codes for comorbidities

Comorbidities	ICD-9-CM code	ICD-10-CM code
Cancer	140~208	C, D0
Diabetes	250	E08~E13
Chronic kidney disease	585, 586	N18
Congestive heart failure	428, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93	I50, I0981, I110, I130, I132
Coronary heart disease	410~414	I20~I25
Liver cirrhosis	571, 571.2, 571.5, 571.6	K703, K717, K746
Chronic obstructive pulmonary disease	491, 492, 518.1, 518.2, 770.2	J41~J44
Dementia	290	F01~F03
Cerebrovascular disease	430~437	G46.3, G46.4, I60~I66, I69
Opportunistic infections		
Cytomegalovirus disease	(078.5	B25
Tuberculosis	010~018	A15~A19
Disseminated Mycobacterium avium complex infection	31.2	A31.2

Pneumocystis jirovecii pneumonia (or pneumocystis carinni pneumonia)	136.3	B59
Cryptococcal meningitis	(321.0	B45.1
Candidiasis	112	B37
Penicillium marneffei infection	117.9	B48.3, B48.8, B49
Herpes zoster	((053)	B02
AIDS-related cancer		
Kaposi sarcoma	176	C46
Non-Hodgkin lymphoma	202.8	C85.8, C85.9
Cervix	180	C53.9

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; AIDS, acquired immune deficiency syndrome.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	11
		(*e*) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-13 12 12-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.