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Mortality and causes of death in people living with HIV in the era of combination antiretroviral therapy compared with the general population in Japan

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Objectives: To determine the mortality and causes of death in people living with HIV (PLHIV) in Japan.

Design: A prospective cohort study at AIDS Clinical Center, Tokyo, which treats approximately 10% of PLHIV in care in Japan.

Methods: Either PLHIV who visited our center for the first time between January 2005 and December 2014 or PLHIV who started their regular visit before January 2005 and visited us between January and March 2005 were included and followed by the end of 2016. Causes of death were defined according to the CoDe protocol.

Results: Two thousand, seven hundred and ninety-seven PLHIV were analysed with total of 18 858 person-years of follow-up, which constitutes 14% of the estimated number of PLHIV in care in Japan. One hundred and sixty-five (5.9%) PLHIV died with all-cause mortality rate of 8.75 per 1000 person-years. All-cause mortality rate for PLHIV in care in Japan was estimated to be 8.75 per 1000 person-years (95% CI 5.53–12.0). Among causes of death, AIDS-defining illnesses accounted for 39% and malignancy contributed to 47%. Standardized mortality ratio (SMR) for all-cause mortality, malignancy-related mortality, and suicide were 5.96 (95% CI 5.05–6.87), 7.76 (95% CI 6.02–9.51), and 3.24 (95% CI 1.54–4.94), respectively. Even among the patients who were diagnosed early or without history of AIDS, SMR was four times higher than the general population.

Conclusion: Mortality of PLHIV, even among those with early diagnosis, is substantially higher than that of the general population in Japan, highlighting the importance of further efforts towards prevention, early diagnosis and prompt treatment initiation.

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Keywords: AIDS, combination antiretroviral therapy, Japan, mortality, people living with HIV

Introduction

Since the introduction of combination antiretroviral therapy (cART), life expectancy of people living with HIV (PLHIV) has substantially increased and several modelling studies suggest that life expectancy of PLHIV diagnosed soon after infection and started on treatment is approaching that of the general population [1–3]. It is also reported that AIDS-related deaths is decreasing whereas non-AIDS related deaths, such as those because

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of non-AIDS malignancy and cardiovascular diseases are increasing among an ageing cohort of PLHIV [4,5].

In Japan, HIV infection is a notifiable disease and when a physician diagnoses HIV infection, it is mandatory that they report to the public health center within 7 days; however, anonymously [6]. By the end of 2015, total cumulative reported number of PLHIV was 27 434 [7,8]. By 2016, approximately 1500 new diagnoses have been reported every year for 10 years and for 2017 and 2018, 1389 and 1288 new diagnoses were reported, respectively, suggesting a decline in the number of new diagnosis [7]. However, reporting of death in PLHIV is not exhaustively defined [6] and it has been substantially underreported [8]. Thus, little data is available for the mortality of PLHIV in Japan. Furthermore, little data on causes of death in PLHIV in Japan is available, which is useful information to help focusing on appropriate interventions to improve morbidity and mortality of PLHIV.

This study aims to elucidate mortality and causes of death in PLHIV in Japan in the era of cART and compare overall and cause-specific mortality with the Japanese general population.

Methods

Study design and patients

We performed a prospective cohort study at AIDS Clinical Center, National Center for Global Health and Medicine (NCGM), Tokyo. AIDS Clinical Center is one of the largest tertiary care centers for HIV infection in Japan with more than 2000 patients with regular visits [9]. As it is estimated that 20 615 PLHIV are retained in care in 2015 in Japan [8], our hospital treats approximately 10% of PLHIV in care. The inclusion criteria were either HIV-infected patients who visited our clinic for the first time between 1 January 2005 and 31 December 2014 or HIV-infected patients who started their regular visit to our clinic before January 2005 and who visited us between 1 January 2005 and 31 March 2005. We applied following exclusion criteria: patients aged less than 20 years at the first visit after January 2005, patients who visited our clinic for a second opinion or those who were referred to other facilities on their first or second visit. The study was approved by the Human Research Ethics Committee of NCGM, and was conducted according to the principles expressed in the Declaration of Helsinki.

Measurements

Patients were followed from the day of enrolment defined as their first visit after 1 January 2005 to the end of follow-up, defined as either the date of death, last date of clinic visit for those who were lost to follow-up or were referred to other hospitals, or 31 December 2016, whichever occurred first. Loss to follow-up was defined as patients who discontinued their visits to our clinic for at least 12 months after the last visit and who were not known to be under the care of any medical facilities or dead [10]. For patients who were referred to other hospitals and were confirmed to have died, such as patients with malignancy in the end-stage referred to the hospice clinic, they were counted as those who died and follow-up period was extended to the date of death.

At our clinic, all patients provide their phone numbers at the first visit, and when they miss the scheduled visit, the 'coordinator nurse' calls the patient to make another appointment, or leave a message to visit if the patient does not answer the phone. If the patient does not visit the clinic after the first call, the nurses continue calling the patient every 3 months up to 1 year [10].

Causes of death was defined according to the Coding of Death in HIV (CoDe) protocol [11,12]. Two physicians who specialize in HIV care (T.N. and K.Ts.) independently established cause of death by thoroughly reviewing the medical chart, and if there was disagreement between the two experts, one additional reviewer (K.Te.) reviewed the chart and established the cause of death. For all death cases because of malignancy, diagnosis of malignancy was confirmed with histopathology. Causes of death were categorized into two groups: AIDS-related (Code 01.1, 01.2, 01) and non-AIDS related (Code 02–92). Also, variables 'malignancy related death' and 'death due to suicide' were made, which included AIDS-related malignancy (01.2) and non-AIDS-related malignancy (04), and suicide (17), respectively [11].

The following clinical data were collected from the medical record: sex, race, HIV transmission route, $CD4^+$ cell count at the first visit to the hospital, nadir $CD4^+$ cell count, history of AIDS prior to or on enrolment, variables at the study enrolment (for patients who started to visit our hospital prior to 1 April 2005, the data between 1 January 2005 and 31 March 2005 were considered as at enrolment: age, HIV viral load, and presence or absence of AIDS-defining infections, AIDS-defining malignancies, and non-AIDS-defining malignancies [11], treatment with cART), development of AIDS-defining infections, AIDS-defining malignancies, and non-AIDS-defining malignancies during observation period and their date, hepatitis B infection defined as positive hepatitis B surface antigen, hepatitis C infection defined as positive hepatitis C antibody. We defined late diagnosis as PLHIV whose $CD4^+$ cell count was less than 200 /μl at the first visit to our hospital [13,14].

Statistical analysis

Characteristics were compared using the Student's *t*-test for continuous variables and using either the χ^2 test or Fisher exact test for categorical variables. The crude mortality rate was calculated by dividing the number of death by person-time at risk. All-cause, AIDS-related,

non-AIDS-related, malignancy-related, and suicide-related mortality per 1000 person-years was calculated for all study patients and also by group. In order to estimate all-cause mortality rate of PLHIV in care in Japan, a two-sided 95% confidence interval (CI) of the crude mortality was estimated in a population of 20 615, the estimated number of PLHIV in care in Japan [8], using the finite population correction [15].

In comparison with the general population, the standardized mortality ratio (SMR) was calculated as the ratio of the observed number of death in the study population to the expected number of death among the general population in Japan. SMR for all-cause, malignancy-related, and suicide-related mortality were determined using 5-year age bands, stratifies by sex-specific vital statistics data for Japan available at the Portal Site of Official Statistics of Japan [16]. The 95% CIs were calculated with normality assumption. The SMRs were calculated for the study patients, patients with and without late diagnosis, and patients with or without history of AIDS prior to or on enrolment.

Hazard ratios and corresponding 95% CIs were estimated with the use of the multivariate Cox proportional hazards model to determine the effect of late diagnosis ($CD4^+$ cell count $<200/\mu l$ at the first visit) on all-cause mortality, adjusted for age and viral load at enrolment, sex, route of infection, race AIDS-defining infection, AIDS-defining malignancy, non-AIDS-defining malignancy at enrolment, and AIDS-defining infection, AIDS-defining malignancy, and non-AIDS-defining malignancy during follow-up.

Sensitivity analysis was performed by excluding PLHIV who died or censored within 60 days after the first visit to our hospital since January 2005, because our hospital is a referral hospital for HIV care and PLHIV with severe morbidity, such as patients with advanced stage of malignancy, might be likely referred to. Also, competing risk analysis was conducted as another sensitivity analysis, to assess the effect of late diagnosis on all-cause mortality, with loss to follow-up treated as a competing risk [17].

Statistical significance was defined with two-sided P value of less than 0.05. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Of 3233 patients screened, 2797 were included as the study patients with total of 18 858 person-years of follow-up. Of the study patients with median age of 36, 2577 (92%) were men, 2539 (91%) were Japanese, and 2185 (78%) were infected with HIV through sex between men, whereas 449 (16%) and 123 (4.4%) were infected through heterosexual contact and contaminated blood product mostly constituted of hemophiliacs, respectively (Table 1). At the enrolment, median $CD4^+$ cell count was 294 (IQR 151–430) and 882 (32%) were on ART. At the last visit to the hospital, 86% of the study patients were with suppressed viral load (<400 copies/ml).

Throughout the study period, there were 165 deaths (5.9%). Causes of death were shown in detail in Table 2. AIDS-related death, including death because of AIDS-defining infection [24 (15%)] and AIDS-defining malignancy [39 (24%)] contributed to 63 (39%) deaths, whereas malignancy-related death including AIDS-defining malignancy [39 (24%)] and non-AIDS-defining malignancy [38 (23%)] contributed to 77 (47%) deaths. Death because of AIDS-defining malignancy is included in both AIDS-related death and malignancy-related death. Suicide contributed to 14 (8.5%) deaths. Among PLHIV with late diagnosis ($CD4^+$ cell count $<200/\mu l$ at the initial visit), mortality was significantly higher than those without late diagnosis [late diagnosis: 110 (9.7%) death out of 1137, non-late diagnosis: 55 (3.3%) death out of 1660, $P<0.001$].

All-cause mortality, malignancy-related mortality, and suicide per 1000 person-years for the study population was 8.75, 4.08, and 0.74, respectively (Table 3). With the assumption of the study cohort being a representative of the entire HIV population in Japan, we estimated the mortality rate for PLHIV in care in Japan to be 8.75 per 1000 person-years (95% CI 5.53–12.0), malignancy-related mortality to be 4.08 (95% CI 1.89–6.29), and suicide to be 0.74 (95% CI, −0.2 to 1.68). All-cause mortality was 17.8 and 13.8 among heterosexual males and those infected through contaminated blood product in this study (Table 3). Non-AIDS-related mortality and malignancy-related mortality were 13.8 and 8.56, respectively, for heterosexual males and were 12.1 and 5.17, respectively, for those infected through contaminated blood product. Among injection drug users ($n=13$) and people with unknown route of transmission ($n=27$), 4 (31%) and 5 (19%) died, respectively.

During the study period, total mortality of this HIV cohort was six times higher than the general population in Japan (SMR 5.96, 95% CI 5.05–6.87; Table 4). Similarly, malignancy-related mortality and suicide were eight and three times higher, respectively, than the general population (malignancy-related mortality: SMR 7.76, 95% CI 6.02–9.51) (suicide: SMR 3.24, 95% CI 1.54–4.94). SMR for all-cause mortality or malignancy-related mortality for the three periods showed a slightly declining trend (Table 4) [all-cause mortality: 2005–2008: 5.93 (95% CI 4.27–7.60), 2009–2012: 5.15 (3.90–6.41), 2013–2016: 4.86 (3.53–6.19)] [malignancy-related mortality: 2005–2008: 7.97 (95% CI 4.71–11.2), 2009–2012: 6.87 (4.41–9.33), 2013–2016: 6.41 (3.84–8.97)]. Sensitivity analysis, which excluded

Table 1. Characteristics and prognosis of the study patients.

	All patients ($n=2797$)	Cohort #1: patients who started their regular visit prior to January 2005 ($n=881$)	Cohort #2: patients who started their visit after January 2005 ($n=1916$)	P value
Age at enrolment[a]	36 (30–44)	37 (32–46)	36 (30–43)	<0.001
Male sex	2577 (92%)	793 (90%)	1784 (93%)	0.006
Japanese	2539 (91%)	829 (94%)	1710 (89%)	<0.001
Asians other than Japanese	136 (4.9%)	26 (3%)	110 (5.7%)	
Others	122 (4.4%)	26 (3%)	96 (5%)	
$CD4^+$ cell count at the first visit to the hospital (/μl)[a]	248 (97–395)	244 (97–403)	249 (97–391)	0.51
CD4 cell count <200/μl at the first visit to the hospital	1137 (41%)	349 (40%)	788 (41%)	0.45
Nadir $CD4^+$ cell count during the observation period (/μl)[a]	162 (56–254)	134 (44–196)	184 (61–285)	<0.001
HIV viral load (log_{10} copies/ml) at enrolment[a,b]	4.30 (2.30–5.01)	2.30 (2.30–3.85)	4.67 (3.91–5.23)	<0.001
Viral load <400 copies/ml at enrolment[b]	800 (29%)	571 (65%)	229 (12%)	<0.001
On ART at enrolment	882 (32%)	613 (70%)	269 (14%)	<0.001
History of AIDS prior to or on enrolment	815 (29%)	262 (30%)	553 (29%)	0.65
AIDS-defining infection at enrolment	522 (19%)	31 (3.5%)	491 (26%)	<0.001
AIDS-defining malignancy at enrolment	103 (3.7%)	12 (1.4%)	91 (4.7%)	<0.001
Non-AIDS defining malignancy at enrolment	28 (1%)	5 (0.6%)	23 (1.2%)	0.15
Development of AIDS-defining infection after enrolment	147 (5.3%)	50 (5.7%)	97 (5.1%)	0.52
Development of AIDS-defining malignancy after enrolment	43 (1.5%)	14 (1.6%)	29 (1.5%)	0.87
Development of non-AIDS-defining malignancy after enrolment	83 (3%)	48 (5.4%)	35 (1.8%)	<0.001
Viral load <400 copies/ml at the last visit[b]	2417 (86%)	806 (92%)	1611 (84%)	<0.001
Route of transmission				
Sex between men	2185 (78%)	613 (70%)	1572 (72%)	<0.001
Heterosexual contact	449 (16%)	161 (18%)	288 (15%)	
Contaminated blood product	123 (4.4%)	104 (12%)	19 (1%)	
Injection drug use	13 (0.5%)	1 (0.1%)	12 (0.6%)	
Unknown	27 (1%)	2 (0.2%)	25 (1.3%)	
positive hepatitis C antibody	258 (9.2%)	148 (17%)	110 (5.7%)	<0.001
Positive hepatitis B surface antigen	238 (8.5%)	89 (10%)	149 (7.8%)	0.049
Smoking	1029 (36.8%)	299 (33.9%)	730 (38.1%)	0.034
Prognosis				
Death	165 (5.9%)	68 (7.7%)	97 (5.1%)	0.001
Referral to other hospitals	684 (25%)	183 (21%)	501 (26%)	
Lost to follow-up	143 (5.1%)	35 (4%)	108 (5.6%)	
Followed to the end of study period	1805 (65%)	595 (68%)	1210 (63%)	
Follow-up period (year)[a]	6.60 (3.16–11.1)	12.0 (7.84–12.0)	5.12 (2.50–8.18)	<0.001

[a]Median (interquartile range).
[b]Data is missing for three.

patients who died or censored within 60 days from the initial visit showed that mortality rate and SMR for total mortality, malignancy-related mortality, and suicide were very similar to those of the study patients (Table 4, Supplementary Table 1, http://links.lww.com/QAD/B675).

Among the study patients with late diagnosis ($CD4^+$ cell count <200 /μl at the initial visit), SMR for all-cause mortality and malignancy-related mortality were 7.75 (6.30–9.20) and 9.68 (7.05–12.3), respectively, whereas those with $CD4^+$ cell count at least 200 /μl at the initial visit, such SMR were 4.08 (3.00–5.16) and 5.66 (3.44–7.88) (Table 4). Among the study patient with history of AIDS prior to or on enrolment, SMR for all-cause mortality and malignancy-related mortality were 8.97 (7.15–10.8) and 13.3 (9.68–16.9), whereas those without history of AIDS, such SMR were 4.16 (3.20–5.12) and 4.25 (2.59–5.92) (Table 4).

In multivariate analysis, late diagnosis ($CD4^+$ cell count <200 /μl at the first visit) was an independent risk factor for all-cause mortality (adjusted hazard ratio 1.96, 95% CI 1.38–2.79, $P < 0.001$) (Table 5). Older age at enrolment, male sex, route of infection other than sex between men, AIDS-defining malignancy at enrolment, non-AIDS-defining malignancy at enrolment, AIDS-defining infection during follow-up, AIDS defining malignancy during follow-up, and non-AIDS defining malignancy during follow-up were also identified to be risk factors for mortality. Very similar results were obtained with sensitivity analyses, which excluded patients who died or censored within 60 days from the initial visit (Supplementary Table 2, http://links.lww.com/QAD/B675) and also with competing risk analysis (Supplementary Table 3, http://links.lww.com/QAD/B675).

Discussion

This single-center study elucidated mortality rate and causes of death in PLHIV in care in Japan and compared

Table 2. The number and specific causes of death, 2005–2016.

	Number of deaths (%)
Total deaths	165 (100%)
AIDS-defining infection	24 (15%)
Pneumocystis pneumonia	6
Progressive multifocal leukoencephalopathy	5
Cytomegalovirus end-organ diseases	3
Toxoplasmosis	2
Disseminated non-tuberculous mycobacteria	2
Others	6
AIDS-defining malignancy	39 (24%)
Diffuse large B-cell lymphoma	17
Burkitt lymphoma	7
Plasmablastic lymphoma	4
Primary central nervous system lymphoma	3
NK/T cell nasal type	2
Kaposi's sarcoma	2
Other non-Hodgkin lymphoma	2
Primary effusion lymphoma	1
Cervical cancer	1
Non-AIDS-defining malignancy	38 (23%)
Hepatocellular carcinoma (6 HCV-related, 1 HBV-related)	7
Lung cancer	6
Colon cancer	5
Acute myeloid leukemia	4
Anal cancer	2
Pancreatic cancer	2
Pharyngeal cancer	1
Tongue cancer	1
Thymic cancer	1
Testicular cancer	1
Lung sarcoma-like cancer	1
Hodgkin lymphoma	1
Gastric cancer	1
Esophageal cancer	1
Cholangiocellular carcinoma	1
Apocrine adenocarcinoma	1
Adenoid cystic carcinoma	1
Gallbladder cancer	1
Non-AIDS, non-malignancy	64 (39%)
Suicide	14 (8.5%)
Chronic viral hepatitis	8 (4.8%)
HCV with cirrhosis	7 (4.2%)
HBV with cirrhosis	1 (0.6%)
Non-AIDS infection	6 (3.6%)
Stroke	4 (2.4%)
Accident	4 (2.4%)
Heart or vascular	3 (1.8%)
Substance abuse	3 (1.8%)
Renal failure	1 (0.6%)
Respiratory disease	1 (0.6%)
Senility	1 (0.6%)
Unknown	19 (12%)

mortality with the general population. Although cART has substantially improved life expectancy of PLHIV, especially in resource-rich setting like Japan, 5.9% of PLHIV in care died with 8.75 deaths per 1000 person-years in the study population, and mortality rate for PLHIV in care in Japan was estimated to be 8.75 (95% CI 5.53–12.0) per 1000 person-years, with the assumption of the study cohort being a representative of the entire HIV population in Japan. Among causes of death, AIDS-defining illnesses including infections and malignancies accounted for 39%, malignancy including AIDS-defining and non-AIDS-defining malignancy for 47%, and suicide for 8.5%. Late diagnosis ($CD4^+$ cell count $<200/\mu l$ at the first visit) and AIDS-defining malignancies were independent risk factors for mortality among others, which could be prevented by early diagnosis and treatment initiation. Compared with the general population, all-cause mortality, malignancy-related mortality, and suicide were 6, 8, and 3 times higher, respectively, in PLHIV in care than the general population. It is notable that even among the study patients with early diagnosis or without history of AIDS, SMR for overall mortality was still high as four. This study showed that even in the era of cART, mortality in PLHIV in care is still substantially higher than the general population in Japan.

There are three strengths in this study. First, this is the first study to date that showed mortality rate and causes of death among PLHIV in care in Japan. 5.9% of PLHIV in care died with 8.75 deaths per 1000 person-years in the study cohort, and mortality rate among PLHIV in care in Japan was estimated to be 8.75 (95% CI 5.53–12.0) per 1000 person-years. Causes of death were determined following the CoDe protocol and all malignancies were histopathologically confirmed. Notably, AIDS death, including AIDS-defining infection and malignancy accounted for 39% of the total death, which warrants need for further strengthening efforts towards early diagnosis and treatment in Japan, since early diagnosis and treatment will decrease AIDS-related mortality, including those caused by infection-related malignancies, such as non-Hodgkin and Hodgkin lymphoma, anal cancer, cervical cancer, and Kaposi sarcoma [18], which accounted for 25% in this study. It is worrisome that in Japan, approximately 30% of new HIV cases has been diagnosed after the onset of AIDS-defining illnesses for at least last 10 years [7]. As 23% of the total death was because of non-AIDS-defining malignancy, the interventions, such as harm reduction (e.g. smoking cessation) should be also emphasized, considering high prevalence of smokers (36.8%) in our cohort.

Suicide accounted for 8.5% of all death, which warrants importance of strengthening mental care and effort towards prevention of suicide among PLHIV in Japan. Although it was difficult to confirm, 11 out of 19 deaths with unknown causes were found dead at home and 3 others outside, who were comparatively young without severe morbidity, suggesting that these might include some suicide or drug abuse cases. The previous report from our hospital showed that at least 8.6% of PLHIV with regular visit had mental illness, highlighting the importance of further strengthening mental care [19].

Second, the present study calculated SMR and showed that compared with sex and age-adjusted general population in Japan, all-cause mortality, malignancy-related mortality, and suicide were six, eight, and three times higher, respectively, in PLHIV in care. National

Table 3. All-cause and cause-specific mortality for the total and subgroups of study patients.

	Total patients ($n=2797$)	MSM ($n=2185$)	Heterosexual male ($n=245$)	Contaminated blood product ($n=123$)	Non-Japanese ($n=258$)	Female ($n=220$)
Total follow-up (person-years)	18858	14468	1518	1161	1450	1669
Deaths (all-causes)						
n	165	105	27	16	12	9
All-cause mortality per 1000 person-years	8.75	7.26	17.8	13.8	8.28	5.39
AIDS-related deaths						
n	63	46	6	2	9	5
Mortality per 1000 person-years	3.34	3.18	3.95	1.72	6.21	3.00
Non-AIDS-related deaths, including unknown causes						
n	102	59	21	14	3	4
Mortality per 1000 person-years	5.41	4.08	13.8	12.1	2.07	2.40
Malignancy-related death						
n	77	49	13	6	4	3
Mortality per 1000 person-years	4.08	3.39	8.56	5.17	2.76	1.80
Suicide						
n	14	12	1	0	0	1
Mortality per 1000 person-years	0.74	0.83	0.66	0	0	0.60
Loss to follow-up						
n	143	104	22	3	19	13
Rate per 1000 person-years	7.58	7.19	14.5	2.58	13.1	7.79

cohort data from England and Wales from 1997 to 2012 showed that 6% of PLHIV died with all-cause mortality of 11.8 per 1000 person-years, with SMR for all-cause mortality and suicide was 5.7 and 2.0, respectively, which included PLHIV who were not linked to care and were conducted during earlier period than the present study [20]. It is encouraging that SMR for all-cause mortality and malignancy-related mortality slightly decreased during observation period.

Third, this study highlights the importance of further promoting prevention effort of HIV infection in Japan by showing that mortality of PLHIV, even with early diagnosis or without history of AIDS, is four times higher than that of the general population. Not to mention the importance of early diagnosis and prompt treatment initiation to improve prognosis of PLHIV, it is important to further promote prevention strategies of HIV infection, including a wide implementation of preexposure prophylaxis (PrEP).

In this study, mortality rate among heterosexual men (17.8 per 1000 person-years) and patients infected through contaminated blood product (13.8) was high compared with patients with other routes of infection. It is difficult to determine what made prognosis of heterosexual male worse in this study. Heterosexual males presented with older age (median 45, IQR 36–55) with advanced HIV infection (55% were with $CD4^+$ cell count $<200/\mu l$). Among 27 deaths, 10 and 3 were because of non-AIDS-defining malignancy and AIDS-defining malignancy, respectively, suggesting that their older age might be associated with development of non-AIDS-defining malignancies, as 6.9% of heterosexual men developed non-AIDS malignancies during follow-up, higher than 3% among the entire study population. Those infected through contaminated blood product are mostly haemophiliacs who were infected with HIV, hepatitis C virus (HCV), and hepatitis B virus around 1983 [21]. Heavy burden of HCV deteriorated prognosis of haemophiliacs in this study, as among 16 deaths, nine were HCV-related, including six HCV cirrhosis and three HCV hepatocellular carcinoma.

How Japan can further promote early diagnosis and treatment initiation and prevention of HIV infection? Efforts to promote HIV diagnostic testing in high-risk population need to be continued and strengthened. Treat all strategy to further implement 'treatment as prevention' and improve prognosis of PLHIV need to be further advocated to healthcare professionals, considering that it was March 2018 when the Japanese HIV treatment guidelines were revised to recommend that all PLHIV should be treated, regardless of their $CD4^+$ cell count [22]. Prior to March 2018, the cut-off $CD4^+$ cell count was $500/\mu l$. There is a strong need to strengthen contact tracing and partner notification, as currently they are up to the effort of only treating physicians and co-medicals and no system to promote contact tracing and partner notification is in place to date [23]. To receive a certificate for financial assistance for out-of-pocket medical expenditure for HIV care including cART, it usually takes at least several months [24] and most PLHIV want to defer cART initiation until they obtain the certificate, resulting in delaying treatment initiation even for those with acute HIV infection, who are often highly infectious because of high viral loads [25,26]. Furthermore, in Japan, PrEP, one of the main pillars for HIV prevention, has been only available as a small scale feasibility study and there is a strong need to expand PrEP.

Table 4. Crude mortality rate and standardized mortality ratio for people living with HIV in Japan compared with the general population: total study population and subgroup analysis.

	Total observation period (2005–2016)	2005–2008	2009–2012	2013–2016
Total patients ($n = 2797$)				
All-cause mortality				
Crude (per 1000 person-years)	8.75	9.86	8.98	7.78
SMR (95% CI)	5.96 (5.05–6.87)	5.93 (4.27–7.60)	5.15 (3.90–6.41)	4.86 (3.53–6.19)
Malignancy-related mortality				
Crude (per 1000 person-years)	4.08	4.50	4.35	3.54
SMR (95% CI)	7.76 (6.02–9.51)	7.97 (4.71–11.2)	6.87 (4.41–9.33)	6.41 (3.84–8.97)
Suicide				
Crude (per 1000 person-years)	0.74	0.86	0.70	0.71
SMR (95% CI)	3.24 (1.54–4.94)	3.19 (0.06–6.31)*	2.38 (0.29–4.46)*	3.09 (0.38–5.80)*
$CD4^+$ cell count <200/μl at the initial visit ($n = 1137$)				
All-cause mortality				
Crude (per 1000 person-years)	14.2	17.6	14.2	12.0
SMR (95% CI)	7.75 (6.30–9.20)	8.33 (5.53–11.1)	6.46 (4.51–8.42)	6.29 (4.18–8.40)
Malignancy-related mortality				
Crude (per 1000 person-years)	6.69	7.71	6.78	5.98
SMR (95% CI)	9.68 (7.05–12.3)	10.4 (5.32–15.5)	7.90 (4.35–11.4)	8.32 (4.36–12.3)
Suicide				
Crude (per 1000 person-years)	0.90	1.65	0.68	0.66
SMR (95% CI)	3.84 (1.00–6.69)*	5.90 (0–12.6)*	2.20 (0–5.25)*	2.90 (0–6.92)*
$CD4^+$ cell count at least 200/μl at the initial visit ($n = 1660$)				
All-cause mortality				
Crude (per 1000 person-years)	4.96	4.91	5.27	4.68
SMR (95% CI)	4.08 (3.00–5.16)	3.59 (1.77–5.41)	3.76 (2.23–5.30)	3.34 (1.75–4.93)
Malignancy-related mortality				
Crude (per 1000 person-years)	2.26	2.46	2.63	1.72
SMR (95% CI)	5.66 (3.44–7.88)	5.18 (1.34–9.01)	5.61 (2.30–8.93)	4.11 (1.07–7.16)
Suicide				
Crude (per 1000 person-years)	0.63	0.35	0.72	0.74
SMR (95% CI)	2.80 (0.73–4.88)*	1.34 (0–3.97)*	1.37 (0–4.05)*	3.24 (0–6.90)*
History of AIDS on or prior to the enrolment ($n = 815$)				
All-cause mortality				
Crude (per 1000 person-years)	16.5	19.0	16.1	15.2
SMR (95% CI)	8.97 (7.15–10.8)	9.05 (5.70–12.4)	7.19 (4.81–9.58)	7.64 (4.90–10.4)
Malignancy-related mortality				
Crude (per 1000 person-years)	9.22	11.7	8.54	8.31
SMR (95% CI)	13.3 (9.68–16.9)	15.4 (8.29–22.5)	9.47 (4.97–14.0)	11.5 (6.03–16.9)
Suicide				
Crude (per 1000 person-years)	0.89	1.46	0.95	0.46
SMR (95% CI)	3.76 (0.46–7.06)*	5.12 (0–12.2)*	3.02 (0–7.22)*	2.02 (0–5.99)*
No history of AIDS on or prior to the enrolment ($n = 1982$)				
All-cause mortality				
Crude (per 1000 person-years)	5.45	6.07	5.98	4.49
SMR (95% CI)	4.16 (3.20–5.12)	4.07 (2.33–5.81)	3.87 (2.49–5.26)	3.20 (1.83–4.57)
Malignancy-related mortality				
Crude (per 1000 person-years)	1.89	1.52	2.59	1.43
SMR (95% CI)	4.25 (2.59–5.92)	2.91 (0.36–5.46)*	5.06 (2.31–7.80)	3.09 (0.80–5.38)*
Suicide				
Crude (per 1000 person-years)	0.68	0.61	0.60	0.82
SMR (95% CI)	3.01 (1.04–4.98)	2.31 (0–5.52)*	2.08 (0–4.43)*	3.56 (0.07–7.05)*
Excluded patients who died or censored within 60 days from the initial visit ($n = 2752$)				
All-cause mortality				
Crude (per 1000 person-years)	7.96	8.37	8.42	7.22
SMR (95% CI)	5.39 (4.52–6.25)	5.09 (3.55–6.63)	4.82 (3.60–6.04)	4.49 (3.20–5.77)
Malignancy-related mortality				
Crude (per 1000 person-years)	3.87	4.08	4.21	3.40
SMR (95% CI)	7.36 (5.66–9.06)	7.28 (4.17–10.4)	6.51 (4.10–8.92)	6.15 (3.64–8.67)
Suicide				
Crude (per 1000 person-years)	0.74	0.86	0.70	0.71
SMR (95% CI)	3.24 (1.54–4.94)	3.19 (0.06–6.31)*	2.38 (0.29–4.47)*	3.10 (0.38–5.81)*

SMR, standard mortality ratio; CI, confidence interval.
*$P > 0.05$.

Table 5. Multivariate analysis to estimate the risk of late diagnosis ($CD4^+$ cell count <200/μl at the first visit) for all-cause mortality.

	Hazard ratio	95% CI	*P* value	Adjusted hazard ratio	95% CI	*P* value
$CD4^+$ cell count <200/μl at the first visit to the hospital	2.88	2.09–3.99	<0.001	1.96	1.38–2.79	<0.001
Age per 1 year	1.06	1.05–1.07	<0.001	1.02	1.01–1.04	<0.001
Male vs. female	1.65	0.84–3.22	0.15	2.30	1.07–4.98	0.008
Non-Japanese vs. Japanese	0.90	0.50–1.62	0.72	1.16	0.62–2.20	0.64
Route of transmission other than same sex contact vs. same sex contact	1.91	1.39–2.63	<0.001	2.22	1.54–3.18	<0.001
HIV viral load at enrolment (per 1 $\log_{10}$/ml increase)	0.96	0.85–1.08	0.45	0.93	0.82–1.06	0.25
AIDS-defining infection at enrolment	2.04	1.45–2.87	<0.001	1.38	0.93–2.06	0.11
AIDS-defining malignancy at enrolment	10.1	6.98–14.5	<0.001	8.47	5.60–12.8	<0.001
Non-AIDS-defining malignancy at enrolment	18.0	10.8–29.8	<0.001	19.6	10.9–35.1	<0.001
AIDS-defining infection during follow-up	3.79	2.55–5.63	<0.001	2.38	1.57–3.60	<0.001
AIDS-defining malignancy during follow-up	2.40	1.13–5.13	0.023	3.12	1.42–6.87	<0.001
Non-AIDS-defining malignancy during follow-up	6.15	4.12–9.18	<0.001	4.65	2.98–7.25	<0.001

CI, confidence interval.

There are several limitations we need to acknowledge. First, being a single-center study, selection bias cannot be completely excluded. PLHIV with severe morbidity might likely be referred to our hospital and mortality shown in this study might overestimate actual number in Japan. We also need to acknowledge that although we estimated mortality rate of all PLHIV in care in Japan based on the results of the present study, the study patients were not randomly selected from the population. However, it is notable that most PLHIV reside in the urban areas, such as Tokyo [23] and the present study covered 14% of total estimated PLHIV who are retained in care in Japan [8], which can make the study population representative of the entire PLHIV population in Japan. Furthermore, sensitivity analyses, which excluded those who died or censored within 60 days after their initial visit showed very similar mortality rates and SMRs (Table 4, Supplementary Table 1, http://links.lww.com/QAD/B675).

Second, 78% of the study population was MSM, reflecting epidemiology of PLHIV in Japan [7]. Because the number of PLHIV with other routes of infection, including female patients, was small, it was difficult to perform thorough analysis among those patients or comparative analysis between MSM and other groups. Third, there is no national database for mortality for PLHIV in Japan and we might not be able to capture all deaths in the cohort. Especially, prognosis of most of those who were lost-to-follow up were unknown. However, a competing risk model, which assessed the effect of late diagnosis on all-cause mortality, with loss to follow-up treated as a competing risk showed very similar results (Supplementary Table 3, http://links.lww.com/QAD/B675).

In conclusion, this prospective study showed that even in the era of cART, 5.9% of PLHIV died with 8.75 deaths per 1000 person-years, and among PLHIV in care in Japan, mortality rate was estimated to be 8.75 (95% CI 5.53–12.0) per 1000 person-years. All-cause mortality, malignancy-related mortality, and suicide were six, eight, and three times higher, respectively, in PLHIV than the general population. Even among the patients who were diagnosed early or without history of AIDS, mortality rate was four times higher than the general population, highlighting the importance of further strengthening efforts towards early diagnosis and prompt treatment initiation, and especially, prevention.

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Conflicts of interest

There are no conflicts of interest.

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