



Survival Trend of HIV/AIDS Patients Starting Antiretroviral Therapy in South Korea between 2001 and 2015

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Purpose: In the recent antiretroviral therapy (ART) era, a large proportion of Korean patients with human immunodeficiency virus (HIV) infection were shown to have low CD4 cell counts at diagnosis and during ART initiation. We investigated the survival trends in patients living with HIV/acquired immunodeficiency syndrome (AIDS) in Korea who started ART in the 2000s, and evaluated the risk factors for mortality to elucidate the association between survival and low CD4 cell counts at ART initiation.

Materials and Methods: Patients with HIV infection who were aged >18 years and had started ART between 2001 and 2015 in the Korean HIV/AIDS cohort study were enrolled. We compared the clinical characteristics, mortality, and causes of death among the enrolled subjects based on the time of ART initiation. Cox regression analysis was used to estimate the adjusted hazard ratios of mortality based on the time of ART initiation.

Results: Among the 2474 patients enrolled, 105 (4.24%) died during the follow-up period of 9568 patient-years. Although CD4 cell counts at the time of ART initiation significantly increased from 161 [interquartile range (IQR), 73.5–303] in 2001–2003 to 273 (IQR, 108–399) in 2013–2015 ($p < 0.001$), they remained low during the study period. The incidence of all-cause mortality was 10.97 per 1000 patient-years during the study period. There was no decreasing trend in mortality between 2001 and 2015. Age >40 years [adjusted hazard ratio, 3.71; 95% confidence interval (CI), 2.35–5.84] and low CD4 counts (<100 cells/mm³: adjusted hazard ratio, 2.99; 95% CI, 1.44–6.23) were significant risk factors for mortality.

Conclusion: Despite excellent HIV care available in the recent ART era, the survival of patients with HIV/AIDS undergoing ART did not improve between 2001 and 2015 in Korea.

Key Words: Anti-retroviral agents, HIV, Republic of Korea, survival

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INTRODUCTION

The overall survival of patients with human immunodeficiency virus (HIV) infection has improved after the introduction and rapid evolution of antiretroviral therapy (ART) over the recent decades.¹⁻⁴ Currently available ART is more effective in viral suppression and less toxic than early ART, with fewer adverse effects. Moreover, patient care, in terms of screening, prophylaxis, and treatment for comorbidities, has improved. Therefore, the life expectancy of patients successfully treated with ART has become closer to that of the general population at similar ages.⁵ This might be related to the patients' increased risk of comorbidities associated with age, such as cardiovascular disease or cancer, which has altered the cause of death. The mortality attributed to acquired immunodeficiency syndrome (AIDS)-defining disease has declined, whereas the proportion of deaths due to non-AIDS causes has increased.⁶⁻⁸

In Korea, although the prevalence and incidence of HIV infection have remained low since the first case of HIV infection reported in 1985, the number of newly confirmed HIV infections has steadily increased every year. According to the Korea Centers for Disease Control and Prevention (KCDC), the number of new infections has increased rapidly since 2010, exceeding 1000 for the first time in 2013 and reaching 1199 in 2016. As a result, the cumulative figure was 121320 in 2017. Men accounted for 95% of the infected individuals, and sexual contact was the major route of infection (>99%).⁹ ART for patients with HIV infection has been scaled up rapidly in Korea over the past 20 years, since the introduction of zidovudine in the country in 1991. Currently, patients with HIV infection are treated with various ART combinations without much financial burden in Korea due to national support. In the early ART era, treatment was initiated when the CD4 cell count was below a certain level, or in the presence of any AIDS-related symptoms. The revised guidelines, published in Korea in 2013, recommend the initiation of treatment after the diagnosis of HIV infection, regardless of the CD4 cell count.¹⁰

In the recent era, improved survival of HIV patients is expected in Korea, owing to the modifications in ART, the national financial support for HIV treatment, as well as the changes in the guidelines for initiating ART. However, whether there have been actual improvements in survival remains arguable, as the proportion of patients with CD4 cell counts ≤ 200 cells/mm³ at diagnosis and during ART initiation has increased in the late ART era.¹¹ Here, we investigated the recent trends in the survival of patients living with HIV/AIDS in Korea who started ART between 2001 and 2015. This study also evaluated the risk factors for mortality to elucidate the association between survival and low CD4 cell counts at ART initiation.

MATERIALS AND METHODS

Study design and participants

We collected data from the Korea HIV/AIDS Cohort Study, a prospective observational cohort study including patients diagnosed with HIV infection from 21 hospitals in Korea. The Korea HIV/AIDS Cohort Study was established in 2006, and we used the data from the baseline and repeated surveys that were collected from December 2006 to December 2016. At the time of baseline survey, we examined the events that occurred throughout the patient's lifetime or on the basis of HIV infection diagnosis. Repeated surveys were conducted, and trained researchers collected data on the events identified since the last survey using a standardized protocol every 6 months. Data on demographic characteristics were collected using a self-reported questionnaire. Data on antiretroviral treatment and adherence, as well as chronic and other diseases, were collected through patient interviews and from medical records. Participants who were lost to follow-up were investigated using nationally reported data to determine whether those participants had died. Additionally, we analyzed the data obtained from the Korea HIV/AIDS Retrospective Cohort Study, which included 2663 patients with HIV infection who never participated in the Korea HIV/AIDS Cohort Study from December 2006 to August 2016. Data were collected from medical records obtained from the 12 participating university-affiliated hospitals. We combined the data from both the Korea HIV/AIDS Cohort Study and the Korea HIV/AIDS Retrospective Cohort Study.

Patients aged >18 years who were confirmed as HIV-positive by Western blot tests were eligible for inclusion in this study. We included patients who received their initial ART between 2001 and 2015, and visited at least one participating hospital. Those who started ART with mono or dual regimens prior to a triple-drug regimen were also included. Participants were followed up from the time of ART initiation. All participants in the prospective cohort provided their written informed consent. Both cohort studies received ethical approval from the Institutional Review Boards of their respective participating institutes.

Data collection

We collected data from both cohorts at the time of ART initiation. The following variables were investigated: age, sex, median CD4 cell counts at the time of initial ART, median HIV viral load at the time of initial ART, median time from HIV infection diagnosis to ART initiation, year of HIV infection diagnosis, and year of ART initiation. Causes of death were classified into categories according to CoDe Project protocol.¹² Deaths were classified as AIDS-related if there was a close association between death and AIDS-defining conditions based on the definition provided by the Centers for Disease Control and Prevention.¹³ Deaths were also considered to be AIDS-related if patients had CD4 cell counts ≤ 200 cells/mm³ at the time of death. Non-AIDS-related deaths were grouped into those caused by infection,

liver disease, malignancy, cardiovascular disease, respiratory disease, accident/suicide/overdose, and others.¹² Information about the cause of death was obtained from the AIDS Management Division of the KCDC, as well as from each participating hospital.

Statistics

Descriptive statistics were used to summarize the causes of death and clinical characteristics at the time of ART initiation according to the year of ART initiation (2001–2003, 2004–2006, 2007–2009, 2010–2012, and 2013–2015). The Cochran-Armitage test for trend was used to determine if there was an association between the period of ART initiation and sex. The Jonckheere-Terpstra test was used to determine if there was a statistically significant association between the period of ART initiation and continuous dependent variables, including median age at the time of initial ART, median CD4 cell counts/viral loads at the time of initial ART, and median time to treatment. To identify a trend in the mortality rate according to the period of ART initiation between 2001 and 2015, we conducted the Mann-Kendall trend test. We used a Cox regression model to analyze the risk factors associated with all-cause mortality. The beginning time point of follow-up was initial ART starting date, and follow-up ended at the date when a participant died. All other participants were censored at the date of their last follow-up visit to the participating clinic. Variables found to be significant in univariate analysis were included in the multivariate model. The relationship between risk factors and mortality were summarized by hazard ratios (HR) and 95% confidence intervals (CI). Continuous variables were presented as medians with inter-

quartile ranges (IQR), and categorical variables were expressed as numbers with percentages. Statistical analyses were performed using SAS Enterprise version 7.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study participants

A total of 3167 participants started ART between 2001 and 2015. Of these, 693 participants were excluded due to missing data for age, CD4 cell counts/viral loads at the time of initial ART, period from HIV infection diagnosis to initial ART, or follow-up duration from the initial ART to death. Thus, a total of 2474 patients with HIV infection who started ART between 2001 and 2015 were included (Fig. 1). The proportion of women was 15.3% in 2001–2003; however, it decreased to 6% in 2013–2015 (p for trend=0.001). The median age decreased from 39 years (IQR 32–44.5 years) in 2001–2003 to 36 years (IQR 28–47 years) in 2013–2015 (p for trend <0.001). Although the median CD4 cell counts at the time of ART initiation increased from 161 cells/mm³ (IQR 73.5–303 cells/mm³) in 2001–2003 to 273 cells/mm³ (IQR 108–399 cells/mm³) in 2013–2015 (p for trend <0.001), they remained low during the study period. There was no significant trend between the period of ART initiation and median HIV viral loads (p for trend=0.379). The median HIV viral loads varied according to the period of ART initiation [73316 (IQR 21601–191500), 50000 (IQR 9700–210000), 48000 (IQR 8520–161000), 65232 (IQR 16300–200000), and 45350 (IQR 11101–157770) copies/mL in 2001–2003, 2004–2006, 2007–2009, 2010–2012, and 2013–2015,

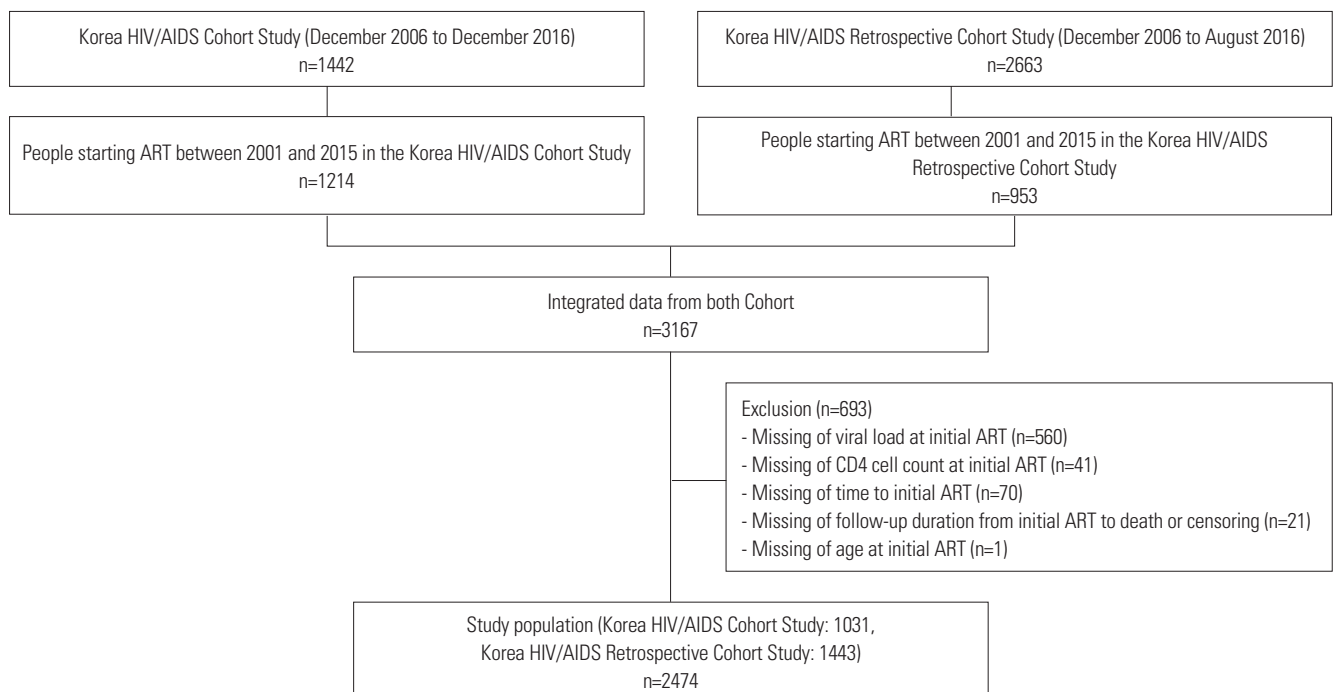


Fig. 1. Flow diagram of study process. HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy.

Table 1. Baseline Characteristics of Patients at the Time of Initiating ART in the Korea HIV/AIDS Cohort Study and Korea HIV/AIDS Retrospective Cohort Study

Variable	2001–2003 (n=144)	2004–2006 (n=327)	2007–2009 (n=615)	2010–2012 (n=686)	2013–2015 (n=702)
Female, n (%)	22 (15.3)	29 (8.9)	38 (6.2)	50 (7.3)	42 (6)
Median age at initial ART, yr (IQR)	39 (32–44.5)	40 (32–48)	40 (32–49)	40 (31–50)	36 (28–47)
Median CD4 counts at initial ART, cells/mm ³ (IQR)	161 (73.5–303)	170 (55–270)	199 (80–280)	196 (69–310)	273 (108–399)
Median viral load counts at initial ART, copies/mL (IQR)	73316 (21601–191500)	50000 (9700–210000)	48000 (8520–161000)	65232 (16300–200000)	45350 (11101–157770)
Initial ART regimen, n (%)					
Monotherapy	3 (2.1)	3 (0.9)	5 (0.8)	3 (0.4)	3 (0.4)
Dual therapy	2 (1.4)	2 (0.6)	18 (2.9)	17 (2.5)	7 (1.0)
Highly active ART	139 (96.5)	322 (98.5)	592 (96.3)	666 (97.1)	692 (98.6)
Year of diagnosis, n (%)					
≤2000	30 (20.8)	19 (5.8)	28 (4.6)	11 (1.6)	5 (0.7)
2001–2003	114 (79.2)	56 (17.1)	37 (6)	22 (3.2)	9 (1.3)
2004–2006		252 (77.1)	130 (21.1)	54 (7.9)	26 (3.7)
2007–2009			420 (68.3)	110 (16)	27 (3.9)
2010–2012				489 (71.3)	88 (12.5)
2013–2015					547 (77.9)
Median time to treatment, months (IQR)	3 (1–12)	3 (1–12)	3 (1–23)	2 (1–19)	1 (1–9)

HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; IQR, interquartile range.

respectively]. Most of the patients (96.3–98.6%) initiated ART which consisted of a minimum of two active drugs from two classes, highly active ART. About 68.3–79.2% of patients started ART during the same period when they were diagnosed with HIV infection. The median time from HIV infection diagnosis to the start of ART decreased from 3 months (IQR 1–12 months) in 2001–2003 to 1 month (IQR 1–9 months) in 2013–2015 (*p* for trend <0.001) (Table 1).

Mortality among people living with HIV/AIDS who started ART between 2001 and 2015

Of the 2474 patients who had started ART between 2001 and 2015, 105 (4.24%) died over a median 3-year follow-up; 11.1% (16/144), 5.2% (17/327), 5.5% (34/615), 4.1% (28/686), and 1.4% (10/702) of patients died in 2001–2003, 2004–2006, 2007–2009, 2010–2012, and 2013–2015, respectively.

The overall mortality rate was 10.97 per 1000 patient-years (PYS) during the entire study period. There was no significantly decreasing trend of mortality in people living with HIV/AIDS who received ART between 2001 and 2015 in Korea (*p* for trend=0.624). The mortality rate, according to the period of ART initiation, decreased from 12.64 per 1000 PYS in 2001–2003 to 8.04 per 1000 PYS in 2004–2006, but then increased until 2012 (12.04 per 1000 PYS in 2007–2009 and 12.73 per 1000 PYS in 2010–2012). The most recent mortality rate was 8.59 per 1000 PYS in 2013–2015 (Table 2). The overall mortality rate was slightly higher in 693 patients who were excluded due to missing data (16.77 per 1000 PYS), and a similar trend of mortality was observed among them (Supplementary Table 1, only online).

Out of 105 deaths, 42 (40%) were AIDS-related (Table 3). Most

Table 2. Mortality among People Living with HIV/AIDS Who Started ART between 2001 and 2015 in the Korea HIV/AIDS Cohort Study and Korea HIV/AIDS Retrospective Cohort Study

Year of starting ART	Median follow-up duration (years)	Follow-up duration (patient-years)	No. of deaths	Mortality rate*
2001–2003	9.7	1266	16	12.64
2004–2006	6	2114	17	8.04
2007–2009	4.3	2825	34	12.04
2010–2012	3	2199	28	12.73
2013–2015	2	1164	10	8.59
Total	3	9568	105	10.97

HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy.

*Mortality rate is the number of deaths per 1000 patient-years.

of these deaths were classified as AIDS-related deaths due to low CD4 cell counts. The specific causes of AIDS-related deaths are shown in Supplementary Table 2 (only online). The proportions of AIDS-related deaths in each period of ART initiation were as follows: 50% in 2001–2003, 52.9% in 2004–2006, 14.7% in 2007–2009, 46.4% in 2010–2012, and 70% in 2013–2015. Although a decreasing trend was observed in the AIDS-related death rate from 2001–2003 to 2007–2009, the “cause unknown” category accounted for the highest proportion of causes of death in the 2007–2009 period (70.6%). Additionally, the proportion of AIDS-related deaths increased over time after the 2007–2009 period, reaching 70% in 2013–2015. Twenty-four (22.9%) deaths were attributable to non-AIDS-related conditions. Malignancy was the most common cause, accounting for 33.3% of non-AIDS-related deaths. Other causes included acute kidney in-

jury and peritoneal leiomyomatosis. The proportion of non-AIDS-related deaths increased from 18.8% in 2001–2003 to 20% in 2013–2015. However, the proportion of AIDS-related deaths was higher than that of non-AIDS-related deaths across all year groups except 2007–2009, for which complete data regarding the causes of deaths were not available.

Risk factors for mortality

In the univariate Cox regression analyses, mortality was significantly associated with age >40 years, CD4 cell counts of <100 and of 100–199 cells/mm³, and viral loads >100000 copies/mL at the initial ART. The multivariate model showed that age >40 years (adjusted HR, 3.71; 95% CI, 2.35–5.84) and low CD4 counts (<100 cells/mm³: adjusted HR, 2.99; 95% CI, 1.44–6.23) were independent risk factors for all-cause mortality in patients who started ART between 2001 and 2015. However, in the multivariate model, calendar year was not statistically significant (Table 4).

DISCUSSION

We investigated the survival trends of people living with HIV/AIDS in Korea between 2001 and 2015. The all-cause mortality rate did not significantly decrease during the study period. Among patients with low CD4 cell counts at the time of ART initiation, AIDS-related mortality was a leading cause of death during the follow-up period. Multivariate Cox regression analyses showed that age >40 years and CD4 cell counts <100 cells/mm³ at initial ART were the factors associated with mortality.

In recent decades, ART has demonstrated great efficacy and few adverse effects compared to earlier treatment regimens, and its use has led to a significant suppression of viral replication. The simplicity of these regimens has contributed to improved short- and long-term adherence. As a result, AIDS-related mortality and all-cause mortality have continued to decrease, even in the late ART era.¹ In Korea, the proportion of patients with HIV infection receiving ART increased from 72% in 2010 to 83% in

2017, and the most frequently used ART regimen involved two nucleotide reverse transcriptase inhibitors plus one protease inhibitor (used in 55.6% of patients; data obtained from Korea Health Insurance Review and Assessment Service). To ensure that no patient remains untreated due to economic reasons, the Korean national health insurance covers HIV-related medical expenses for those who are registered in the national system,

Table 4. Cox Proportional Hazards Analysis for Mortality

Variable	n (%)	Univariate HR (95% CI)	Multivariate HR (95% CI)
Age at initial ART (yr)			
≤40	1355 (54.8)	1	
>40	1119 (45.2)	3.83 (2.46–5.95)	3.59 (2.3–5.59)
Sex			
Male	2293 (92.7)	1.34 (0.62–2.88)	1.29 (0.59–2.8)
Female	181 (7.3)	1	
Median CD4 counts at initial ART (cells/mm ³)			
<100	706 (28.5)	3.67 (1.74–7.71)	2.56 (1.17–5.61)
100–199	475 (19.2)	1.78 (0.78–4.06)	1.38 (0.59–3.22)
200–349	832 (33.6)	1.43 (0.65–3.17)	1.27 (0.57–2.85)
≥350	461 (18.6)	1	
Median viral load counts at initial ART (copies/mL)			
<10000	568 (23)	1	
10000–100000	1036 (41.9)	1.15 (0.66–2.01)	1.05 (0.59–1.86)
>100000	870 (35.2)	1.92 (1.12–3.27)	1.41 (0.8–2.49)
Year of initial ART			
2001–2003	144 (5.8)	1.36 (0.59–3.15)	1.23 (0.53–2.86)
2004–2006	327 (13.2)	1.08 (0.51–2.32)	0.87 (0.4–1.88)
2007–2009	615 (24.9)	1.48 (0.76–2.88)	1.23 (0.62–2.42)
2010–2012	686 (27.7)	1.57 (0.81–3.06)	1.27 (0.65–2.48)
2013–2015	702 (28.4)	1	
Median time until starting ART since HIV diagnosis (month)			
≤2	1078 (43.6)	1	
>2	1396 (56.4)	0.74 (0.51–1.07)	0.98 (0.66–1.45)

HR, hazard ratio; CI, confidence interval; ART, antiretroviral therapy; HIV, human immunodeficiency virus.

Table 3. Causes of Death among Patients according to Year of Initiating Antiretroviral Therapy in the Korea HIV/AIDS Cohort Study and Korea HIV/AIDS Retrospective Cohort Study

Causes of death	2001–2003 (n=16)	2004–2006 (n=17)	2007–2009 (n=34)	2010–2012 (n=28)	2013–2015 (n=10)
AIDS, n (%)	8 (50)	9 (52.9)	5 (14.7)	13 (46.4)	7 (70)
Non-AIDS, n (%)	3 (18.8)	7 (41.2)	5 (14.7)	7 (25)	2 (20)
Infection				1 (3.6)	1 (10)
Liver disease		1 (5.9)			
Malignancy		2 (11.8)	4 (11.8)	1 (3.6)	1 (10)
Cardiovascular disease	1 (6.3)	1 (5.9)		3 (10.7)	
Respiratory disease	2 (12.5)	2 (11.8)	1 (2.9)	1 (3.6)	
Accident/suicide/overdose					
Others*		1 (5.9)		1 (3.6)	
Unknown, n (%)	5 (31.3)	1 (5.9)	24 (70.6)	8 (28.6)	1 (10)

HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

*Other causes included acute kidney injury and peritoneal leiomyomatosis.

after the confirmation of HIV infection. However, we could not observe an improved survival trend in this study, which may be explained by the low CD4 cell counts at ART initiation. The baseline CD4 cell count at ART initiation is one of the most important prognostic factors, as low CD4 cell counts at initiation are associated with high mortality.¹⁴ Domestic guidelines, which were revised in 2013, removed the recommendation of a CD4 count threshold for ART initiation, which may have led to a decrease in the median time from HIV infection diagnosis to treatment initiation, as well as increased median CD4 counts at the initial ART. Nonetheless, until recently, CD4 cell counts at the time of ART initiation remained low in our cohort. One study investigated the trends of CD4 cell counts at HIV infection diagnosis in Korea, and found that CD4 cell counts at the time of HIV infection diagnosis remained low between 2001 and 2015 (median CD4 cell count at the initial HIV infection diagnosis, 247 cells/mm³). According to that study, the proportion of patients with CD4 cell counts ≤ 200 cells/mm³ at the time of HIV infection diagnosis increased gradually, reaching 51% in 2010–2012.¹¹ These findings indicate that a large proportion of patients in Korea continued to start their treatment late due to a delayed diagnosis rather than deferred ART.

In contrast to our results, CD4 cell counts at the initial ART increased from 173 cells/mm³ before 2007 to 302 cells/mm³ after 2011 in Asia as a whole.¹⁵ The proportion of late presenters (defined as patients with CD4 cell count ≤ 200 cells/mm³ at diagnosis) decreased from 79.1% before 2007 to 36.3% after 2011, which may have contributed to improved survival over the years in this region.¹⁶ According to this study, AIDS-related mortality was the main cause of death before 2007, but there was a decrease in the AIDS-related mortality rate over time. Another study based on data from the UK Collaborative HIV Cohort Study showed similar results. The proportion of patients with CD4 cell count ≤ 200 cells/mm³ at the start of ART decreased from 67% in 1996–1999 to 49% in 2006–2008, and the mortality rate decreased during the same period.¹⁷

Several factors have been reported to be associated with late presentation in Korea.¹⁸ Among them, older age was shown to be an important factor in previous studies,^{19–21} as well as in this study (Supplementary Table 3, only online). This may be due to a lack of knowledge about HIV infection among older patients in Korea. Indeed, the current Korean educational and preventive programs regarding HIV infection are primarily targeted to adolescents and young adults; therefore, older people may have little knowledge about HIV infection. Additionally, the fear of stigma may contribute to a delayed diagnosis and treatment. According to a 2016 survey by the National Human Rights Commission of Korea, the fear of an HIV infection diagnosis becoming known to others and possible discrimination due to HIV infection were major difficulties for people living with HIV/AIDS.

Our study had several limitations. First, the size of the study population was small. However, considering the low prevalence of HIV infections in Korea, our data, derived from the largest co-

hort in Korea, were representative of people living with HIV/AIDS in Korea. Second, we did not include some covariates due to missing data. Therefore, the effect of confounding factors was not fully controlled. Third, in 2007–2009, the period when the cohort had the lowest proportion of AIDS-related deaths during the study period, the cause of death accounting for the largest proportion of deaths was “unknown.” For mortality data in HIV patients, we used the death report data from the AIDS Management Division of the KCDC, as well as medical records in the hospitals; however, unlike hospital medical records, the death report data only indicated whether the patients had died and the time of death, but not the cause of death. Since a large proportion of mortality data for 2007–2009 were derived from death report data, the causes of death were unknown for the largest proportion of deaths in that period.

Recent guidelines recommend early initiation of ART regardless of CD4 cell counts, which confers a survival benefit.^{10,22,23} However, CD4 cell counts at the initial ART are still low in Korea due to late diagnosis. AIDS-related mortality remains the leading cause of death, despite excellent HIV care available in the recent ART era. Early initiation of ART in patients with high CD4 cell counts remains a challenge to the Korean public health system. National efforts to reduce the proportion of late presenters must be implemented via the promotion of HIV testing among community residents and other vulnerable groups in various settings. It is also necessary to increase awareness about HIV infection through the expansion of educational and preventive programs directed toward older people and to strengthen the linkage to medical institutions, considering the age-specific characteristics of the subjects.

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