Causes of Death in People Living with Human Immunodeficiency Virus in Türkiye: A Multicentre Retrospective Study

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Abstract

Purpose

Effective antiretroviral therapy has significantly reduced mortality rates among people living with HIV (PWH) and has altered the distribution of causes of death. We aimed to investigate trends in causes of death among PWH over time**.**

Methods

We investigated all reported deaths in the Turkish Clinical Microbiology and Infectious Diseases Society HIV Cohort. Causes of death were categorized and analyzed across four time periods: 1997–2006, 2007–2014, 2015–2019, and 2020–2023. Factors associated with HIV/AIDS-related causes of death were compared to other causes of death.

Results

A total of 9,334 PWH were followed, of which 414 deaths (4.4%) occurred, including 44 (11.6%) among individuals assigned female at birth. The most common causes of death were AIDS-related illnesses (57.7%), non-AIDS-related cancers (11.1%), and cardiovascular diseases (9.9%).

Among causes of death, the rate of AIDS-related diseases has declined over the years ($p<0.001$). Rates of non-AIDS-related cancers ($p=0.013$) and non-AIDS-related infections ($p=0.008$) have increased, and deaths due to comorbid conditions such as cardiovascular diseases have remained stable ($p=0.193$).

In multivariate analysis, AIDS-related deaths were significantly associated with an increased risk in individuals who had an AIDS-defining illness at baseline. The rate of AIDS-related deaths declined in later periods compared to 1997–2006. AIDS-related deaths decreased with older age at HIV diagnosis. The rate of AIDS-related deaths was less frequent among men who have sex with men, smokers, and ex-smokers, individuals on antiretroviral therapy, those with higher CD4 counts, and individuals with comorbid diseases.

Conclusions

Among all deaths, AIDS-related deaths have declined. In contrast, the proportion of deaths attributed to non-AIDS-related cancers has increased, and the mortality rate from cardiovascular disease has remained unchanged over the years. Therefore, it is crucial to implement interventions that address comorbid conditions, particularly by enhancing the management of cardiovascular disease and cancer.

Keywords: HIV/AIDS; cause of death; cancer; infection; cardiovascular disease

Introduction

Since the introduction of effective antiretroviral therapy (ART) in 1996, AIDS-related morbidity and mortality rates have significantly decreased among people living with human immunodeficiency virus (HIV; PWH), leading to corresponding increases in life expectancy [1, 2]. ART has averted approximately 20.8 million AIDS-related deaths since the beginning of the HIV epidemic [3].

With successful viral suppression achieved through ART, non-AIDS-related deaths due to conditions such as cardiovascular disease and non-AIDS-defining cancers have become more predominant recently [4, 5]. The causes of death may vary depending on the timing of the HIV diagnosis and the initiation of ART, adherence to treatment and to clinical visits and the socioeconomic conditions of the individual as well as the country they live in. Therefore, each country must identify the leading causes of death in PWH to implement targeted interventions to reduce mortality [6, 7]. Understanding the causes of death and the factors influencing mortality in PWH is essential for planning and developing policies for early diagnosis, early access to treatment, close follow-up and preventive measures. However, data on the causes of death in PWH living in Türkiye is unavailable. The aim of this study was to define the trends in the causes of death among PWH in Türkiye over time**.**

Methods

Study Design and Population

This retrospective study analyzed demographic characteristics, psychosocial factors, laboratory results, treatments, and causes of death among PWH aged 16 years and older. Data were obtained from the Turkish Clinical Microbiology and Infectious Diseases Society HIV Cohort, a multicenter national cohort.

The study included PWH who presented to 16 centers across the country between January 1997 and July 2023 and died during follow-up. Available immunological and virological data at baseline and within the last 3 months before death were extracted from medical records. In addition, data for other underlying and contributing causes of death were analyzed. We grouped the causes of death into the following categories: AIDS-related, cardiovascular disease-related, kidney failure-related, non-AIDS cancers (excluding Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer), non-AIDS infections (infections other than AIDS-defining opportunistic infections), suicide, and other.

Statistical Analysis

We described the total numbers and proportions of cause-of-death categories stratified by calendar years. Data were grouped into follow-up periods: 1997–2006, 2007–2014, 2015–2019, and 2020–2023.

The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. Patients' characteristics, such as n (percent) or median (interquartile range [IQR]) for categorical and continuous variables, respectively,

were compared among groups using chi-square or Kruskal-Wallis H tests, as appropriate. The Bonferroni-corrected Mann-Whitney U test was used to compare groups in pairs.

Factors associated with HIV/AIDS-related causes of death were compared to other causes of death. Covariates included in the multivariable models were selected based on their significance in univariable analysis ($P < 0.05$) and clinical relevance. Forest plots were created to display the pooled results. Statistical analyses were conducted using SPSS for Macos, version 30.

RESULTS

Patient Characteristics

The cohort included 9,334 PWH followed-up between January 1997 and July 2023, with 414 deaths (4.4%) recorded, and the status of 914 individuals was unknown. Among those who died, 44 (10.6%) were individuals assigned female sex at birth. The most common mode of HIV acquisition was heterosexual contact (61.8%), followed by men who have sex with men (gay and bisexual men) in 105 cases (25.4%) and intravenous drug use in 11 cases (2.7%) (Table 1). Overall, 156 (37.7%) were active smokers, 83 (29.2%) were ex-smokers, and 46 (11.1%) were heavy drinkers (consuming five or more drinks per day). Twenty-five (6%) cases had chronic hepatitis B and 9 (2.2%) cases chronic hepatitis C (Table 1). The median age at diagnosis was 44 years (IQR 35–53), while the median age at death was 47 years (IQR: 38–56). The death age increased over time, from 37.5 years (IQR: 32.5–45) in 1997–2006 to 49 years (IQR: 42–61) in 2020–2023 (Table 1). On average, the time from HIV diagnosis to death was 2.95 years (±4.24). In 184 cases (44.4%), death occurred within a year of diagnosis.

At baseline, the median CD4+ T cell count in 361 cases was 100 cells/mL. Among those, 250 (69.3%) had a CD4+ T cell count lower than 200 cells/mL. The median HIV-1 RNA level in 322 cases was 235000 copies/mL. ART was initiated in 333 cases (80.4%), with a median duration of 15 months. AIDS-defining illness was present in 289 cases (69.8%), and 62 (14.9%) had more than one AIDS-defining illness at the time of initial diagnosis. The median CD4+ T cell count was 95 cells/mL (n = 303) before death. The median viral load was 948.5 copies/mL (n = 302) (Table 1).

Table 1 Distribution of Demographic, Clinical, and Laboratory Characteristics of Patients According to Year of Death

Characteristics (N=414)	**Year of death**					**p-value**	**Post-HOC***
	Total (N=414)	**1997-2006 (n=80)**	**2007-2014 (n=86)**	**2015-2019 (n=132)**	**2020-2023 (n=116)**		
	n (%) or Median (Q25-Q75)	**n (%) or Median (Q25-Q75)**	**n (%) or Median (Q25-Q75)**	**n (%) or Median (Q25-Q75)**	**n (%) or Median (Q25-Q75)**		
Gender						0.153	
Male	370 (89.4)	70 (87.5)	76 (88.4)	114 (86.4)	110 (94.8)		
Female	44 (10.6)	10 (12.5)	10 (11.6)	18 (13.6)	6 (5.2)		

Median age of diagnosis, years	44 (35-53)	**35 (30-43.5)**	**43 (32-52)**	**48 (40-56)**	**47 (37-56)**	**<0.001**	**1<2;1<3; 1<4**
Median age of death, years	47 (38-56)	**37.5 (32.5-45)**	**47.5 (39-54)**	**50 (41-59)**	**49 (42-61)**	**<0.001**	**1<2;1<3; 1<4**
Median time from diagnosis to death, years	1 (0-5)	**1 (0-4)**	**1 (0-7)**	**0 (0-3)**	**1 (0-5)**	**0.042**	**3<2;3<4**
Intravenous substance use	11 (3.3)	3 (5.3)	2 (3.1)	2 (1.8)	4 (4.1)	0.644	
Non-intravenous substance use	24 (7.4)	4 (7)	3 (4.8)	7 (6.3)	10 (10.6)	0.509	
Weight before death	63 (55-73)	**55 (50-68)**	**59.5 (53.5-70)**	**65 (55-73)**	**69 (58-7.,5)**	**<0.001**	**1<3;1<4**
HIV transmission route						**<0.001**	
Heterosexual	256 (61.8)	**64 (80)**	**58 (67.4)**	**79 (59.8)**	**55 (47.4)**		
Homosexual	63 (15.2)	**6 (7.5)**	**14 (16.3)**	**23 (17.4)**	**20 (17.2)**		
Bisexual	42 (10.1)	**6 (7.5)**	**7 (8.1)**	**9 (6.8)**	**20 (17.2)**		
Blood product	3 (0.7)	**2 (2.5)**	**1 (1.2)**	**0 (0)**	**0 (0)**		
Other	27 (6.5)	**2 (2.5)**	**1 (1.2)**	**14 (10.6)**	**10 (8.6)**		
Unknown	23 (5.6)	**0 (0)**	**5 (5.8)**	**7 (5.3)**	**11 (9.5)**		
Smoking						**0.003**	
Non-smoker	45 (15.8)	**16 (29.6)**	**5 (9.1)**	**9 (9.8)**	**15 (18.1)**		
Smoker	156 (54.9)	**32 (59.3)**	**34 (61.8)**	**49 (53.3)**	**41 (49.4)**		
Ex-smoker	83 (29.2)	**6 (11.1)**	**16 (29.1)**	**34 (37)**	**27 (32.5)**		
Cigarette use (pack/year)	20 (12-30)	20 (12-30)	20 (10-33)	20 (12-30)	25 (15-40)	0.471	
Excessive use of alcohol (>5 alcohol/day)	46 (14.3)	**4 (6.6)**	**8 (13.1)**	**11 (10.4)**	**23 (24.5)**	**0.006**	
Chronic HBV infection	25 (6.1)	8 (10)	8 (9.4)	5 (3.8)	4 (3.4)	0.094	
Chronic HCV infection	9 (2.2)	3 (3.8)	2 (2.4)	3 (2.3)	1 (0.9)	0.597	
Use of ART	333 (80.4)	**46 (57.5)**	**69 (80.2)**	**118 (89.4)**	**100 (86.2)**	**<0.001**	
Duration of use ART, months	15 (4-41)	8 (2-24)	16,5 (5-43.5)	16 (5-48)	17.5 (2.5-58.5)	0.188	

Treatment compliance	208 (72)	**24 (55.8)**	**32 (56.1)**	**82 (79.6)**	**70 (81.4)**	**<0.001**	
Baseline median CD4 count, cells/µL	100 (30-253)	85.5 (30-151.5)	128 (30-270)	88.5 (30-267)	111.5 (29.5-280.5)	0.474	
Baseline CD4 percent	10 (5-16)	11 (5.5-16.5)	9 (5-17)	10 (4-16)	11 (5-16.5)	0.934	
Baseline HIV-RNA count, x10^3, copies/mL	235 (75-1108.5)	**159.4 (64.5-750)**	**173.5 (66.1-824)**	**227.6 (70.9-1047.4)**	**318 (132.2-2037.7)**	**0.037**	**1<4;2<4**
AIDS defining disease[#]	289 (69.8)	**70 (87.5)**	**59 (68.6)**	**86 (65.2)**	**74 (63.8)**	**0.002**	
Salmonella bacteremia	2 (0.8)	0 (0)	0 (0)	1 (1.4)	1 (1.4)	0.683	
Progressive multifocal leukoencephalopathy	13 (3.6)	3 (3.9)	2 (2.5)	4 (3.7)	4 (4.3)	0.930	
Mycobacterium avium complex	6 (1.7)	0 (0)	0 (0)	2 (1.9)	4 (4.3)	0.086	
Recurrent bacterial pneumonia	19 (5.3)	**0 (0)**	**2 (2.5)**	**8 (7.3)**	**9 (9.7)**	**0.018**	
HIV wasting syndrome	11 (3.1)	**7 (9.1)**	**1 (1.2)**	**1 (0.9)**	**2 (2.2)**	**0.007**	
Bronchi, trachea or lung candidiasis	13 (3.6)	2 (2.6)	2 (2.5)	4 (3.7)	5 (5.4)	0.714	
Cryptosporidiosis	11 (3.1)	**6 (7.9)**	**3 (3.7)**	**0 (0)**	**2 (2.2)**	**0.021**	
Cytomegalovirus	22 (6.1)	5 (6.5)	3 (3.7)	7 (6.5)	7 (7.4)	0.764	
Cryptococcal meningitis	26 (7.2)	10 (12.8)	2 (2.5)	7 (6.5)	7 (7.4)	0.090	
HIV dementia	13 (3.6)	4 (5.1)	3 (3.7)	4 (3.7)	2 (2.1)	0.773	
Pneumocystis pneumonia	46 (12.8)	9 (11.5)	9 (11.1)	12 (11.1)	16 (17)	0.570	
Non-Hodgkin Lymphoma	40 (11.1)	3 (3.8)	7 (8.6)	15 (13.9)	15 (16)	0.051	
Cerebral toxoplasmosis	29 (8.1)	4 (5.1)	7 (8.6)	10 (9.3)	8 (8.5)	0.751	
Esophageal candidiasis	43 (11.9)	**19 (24.4)**	**8 (9.9)**	**9 (8.3)**	**7 (7.4)**	**0.002**	

Kaposi's sarcoma	29 (8)	8 (10.3)	6 (7.4)	6 (5.6)	9 (9.6)	0.623	
Tuberculosis	77 (21.4)	**24 (31.2)**	**23 (28.4)**	**19 (17.8)**	**11 (11.7)**	**0.005**	
Solid organ cancer	6 (1.7)	**1 (1.4)**	**0 (0)**	**0 (0)**	**5 (5.3)**	**0.013**	
Last CD4 count, cells/µL	95 (24-320)	**46 (14-103.5)**	**63 (22-219)**	**140.5 (34-368)**	**149 (42-421)**	**<0.001**	**1<3;1<4**
Last CD4 percent	12 (5.1-21.6)	**6 (3-11)**	**10 (3-20)**	**15 (9.5-23)**	**14 (7.5-25)**	**<0.001**	**1<3;1<4**
Last HIV-RNA count copies/mL	948.5 (0-124000)	**100000 (20000-743000)**	**7810 (104-278300)**	**77 (0-26500)**	**50.5 (0-64355)**	**<0.001**	**4<1;4<2;3<1;3<2**
Last Hemoglobin count, g/dL	9.8 (8.4-11.8)	10 (8.7-11)	10 (9.1-11.6)	9.7 (8.2-11.9)	9.6 (8.1-12.1)	0.903	
Diabetes mellitus	36 (8.7)	**1 (1.3)**	**7 (8.1)**	**16 (12.1)**	**12 (10.3)**	**0.047**	
Cardiovascular disease	43 (10.7)	**2 (2.5)**	**7 (8.1)**	**20 (15.9)**	**14 (12.8)**	**0.017**	
Chronic liver disease	25 (6)	**7 (8.8)**	**10 (11.6)**	**5 (3.8)**	**3 (2.6)**	**0.025**	
Chronic kidney disease	29 (7)	1 (1.3)	5 (5.8)	10 (7.6)	13 (11.3)	0.056	
Hypertension	53 (12.9)	**1 (1.3)**	**9 (10.5)**	**25 (19.1)**	**18 (15.7)**	**0.002**	
Non-AIDS related cancer	57 (13.9)	**2 (2.5)**	**13 (15.1)**	**23 (17.8)**	**19 (16.5)**	**0.011**	
Dyslipidemia	40 (10.1)	**0 (0)**	**7 (8.1)**	**18 (14.4)**	**15 (14.3)**	**0.003**	
History of depression	73 (18)	21 (26.3)	13 (15.1)	23 (18.1)	16 (14.2)	0.151	

*: Significance values have been adjusted by the Bonferroni correction for multiple tests.

[#]: Some patients have more than one AIDS-defining illness

The most common causes of death were AIDS (239 deaths; 57.7%), non-AIDS-related malignancies (48 deaths; 11.6%), and cardiovascular diseases (41 deaths; 9.9%). Opportunistic infections caused death in 137 patients (33.1%), with tuberculosis being the most frequent infectious cause (Table 2).

Among causes of death, the rate of AIDS-related diseases has declined over the years, while rates of non-AIDS-related cancers and infections have increased, and deaths due to comorbid conditions such as cardiovascular diseases have remained stable. Among causes of death, the rate of AIDS-related diseases has declined over the years ($p<0.001$). In contrast, rates of non-AIDS-related cancers ($p=0.013$) and non-AIDS-related infections

(p=0.008) have increased, and deaths due to comorbid conditions such as cardiovascular diseases have remained stable (p=0.193) (Table 2).

AIDS-related deaths occurred at younger ages than non-AIDS-related deaths (43.83 years vs. 53.14 years; p<0.0001). Deaths from AIDS-related cancer also occurred at younger ages, compared to deaths from non-AIDS-related cancer (45.79 years vs. 55.81 years; p<0.0001).

The most common cause of death among individuals living with HIV was cancer, accounting for 27.3% of deaths. Of these, 66 deaths (15.9%) were due to AIDS-related cancers, while 48 (11.6%) were due to non-AIDS-related cancers. One patient died due to lung cancer and non-Hodgkin lymphoma. Among AIDS-related cancers, the leading causes of death were non-Hodgkin lymphoma (44 deaths), Kaposi's sarcoma (21 deaths), and cervical cancer (1 death). Non-AIDS-related cancers included solid cancers (39 deaths), hematological cancers (6 deaths), and Hodgkin's lymphoma (4 deaths). The most common solid cancer was lung cancer, which accounted for 19 deaths (Table 2).

Tablo 2 Causes of Death from 1997 to 2023, Classified by Year of Death

Characteristics[β] (N=414)	**Year of death**					**p-value**
	Total (N=414)	**1997-2006 (n=80)**	**2007-2014 (n=86)**	**2015-2019 (n=132)**	**2020-2023 (n=116)**	
	n (%) or Median (Q25-Q75)	**n (%) or Median (Q25-Q75)**	**n (%) or Median (Q25-Q75)**	**n (%) or Median (Q25-Q75)**	**n (%) or Median (Q25-Q75)**	
AIDS-related death	239 (57.7)	**71 (88.8)**	**51 (59.3)**	**63 (47.7)**	**54 (46.6)**	**<0.001**
AIDS-related cancer[µ]	66 (15.9)	13 (16.3)	16 (18.6)	17 (12.9)	20 (17.2)	0.675
Non-Hodgkin Lymphoma	44 (10.6)	5 (6.3)	11 (12.8)	13 (9.8)	15 (12.9)	0.428
Kaposi's sarcoma	21 (5.1)	7 (8.8)	5 (5.8)	4 (3)	5 (4.3)	0.304
Invasive servikal cancer	1 (0.3)	1 (1.3)	0 (0)	0 (0)	0 (0)	
HIV wasting syndrome[£]	36 (8.7)	**23 (28.7)**	**8 (9.3)**	**3 (2.3)**	**2 (1.7)**	**<0.001**
HIV dementia[£]	8 (1.9)	**5 (6.3)**	**1 (1.2)**	**2 (1.5)**	**0 (0)**	**0.014**
Opportunistic infection[β£]	137 (33.1)	**40 (50.0)**	**32 (37.2)**	**28 (28.8)**	**27 (23.3)**	**0.001**
Tuberculosis	60 (14.5)	**22 (27.5)**	**19 (22.1)**	**14 (10.6)**	**5 (4.3)**	**<0.001**
Pneumocystis pneumonia	27 (6.5)	5 (6.3)	5 (5.8)	6 (4.5)	11 (9.5)	0.458
Cryptococcal meningitis	19 (4.6)	**10 (12.5)**	**1 (1.2)**	**4 (3)**	**4 (3.4)**	**0.002**
Cerebral toxoplasmosis	17 (4.1)	4 (5.0)	5 (5.8)	6 (4.5)	2 (1.7)	0.469
Cytomegalovirus	9 (2.2)	2 (2.5)	2 (2.3)	4 (3.0)	1 (0.9)	0.695
Progressive multifocal leukoencephalopathy	9 (2.2)	2 (2.5)	1 (1.2)	4 (3)	2 (1.7)	0.797
Mycobacterium avium complex	7 (1.7)	0 (0)	1 (1.2)	3 (2.3)	3 (2.6)	0.503

Bacterial pneumonia	5 (1.2)	0 (0)	1 (1.2)	1 (0.8)	3 (2.6)	0.384
Non-AIDS related cancer[μ]	48 (11.6)	**2 (2.5)**	**8 (9.3)**	**22 (16.7)**	**16 (13.8)**	**0.013**
Hodgkin Lymphoma	4 (0.5)	0 (0)	1 (1.2)	3 (2.2)	0 (0)	0.622
Solid organ cancer	38 (9.2)	**1 (1.3)**	**7 (8.1)**	**15 (11.4)**	**15 (12.9)**	**0.031**
Hematologic cancer	6 (1.4)	2 (2.5)	0 (0)	3 (2.3)	1 (0.9)	0.425
Non-AIDS infections[α]	33 (8.0)	**1 (1.3)**	**4 (4.7)**	**12 (9.1)**	**17 (14.7)**	**0.008**
Cardivascular disease	41 (9.9)	5 (6.3)	5 (5.8)	17 (12.9)	14 (12.1)	0.193
Kidney failure	12 (2.9)	0 (0)	3 (3.5)	6 (4.5)	3 (2.6)	0.283
Suicide	6 (1.4)	1 (1.3)	0 (0)	3 (2.3)	2 (1.7)	0.578
Other[#]	36 (8.7)	**1 (1.3)**	**12 (14.0)**	**9 (6.8)**	**14 (12.1)**	**0.013**

[β]: Some cases had more than one opportunistic infection cause of death

[μ]: One patient had both non-Hodgkin lymphoma and lung cancer

[α]: Sepsis, COVID-19, infective endocarditis, candidemia

[£]: Some cases had opportunistic infections, dementia, or wasting syndrome simultaneously.

[#]**:** Accident, cirrhosis, homicide, cerebrovascular stroke, subarachnoid hemorrhage, gastrointestinal bleeding, pancreatitis, trauma, bowel perforation, drug overdose, undiagnosed.

The results of the multivariate analysis comparing HIV/AIDS-related causes of death with other causes are presented in Table 3 and Figure 1. The analysis showed a significantly higher risk of AIDS-related death among individuals with an AIDS-defining illness at baseline. The rate of AIDS-related deaths declined in later periods compared to 1997–2006. The rate of AIDS-related death rate decreased with increasing age at HIV diagnosis and was lower among men who have sex with men. Individuals on ART and those with higher CD4 counts had lower rates of AIDS-related deaths. AIDS-related deaths were lower among individuals with diabetes mellitus, chronic cardiovascular disease, chronic renal failure, or hypertension. AIDS-related deaths were less frequent among smokers and ex-smokers than non-smokers. In contrast, non-AIDS-related deaths were higher among smokers (40.4%) and ex-smokers (61.4%) compared with non-smokers (22.2%) ($p < 0.001$).

Table 3 Risk factors affecting AIDS-related deaths

	Odds ratio (95%Cl)	**p-value**
Year of death		
1997-2006	Reference	Reference
2007-2014	**0.185 (0.082-0.418)**	**<0.001**
2015-2019	**0.116 (0.053-0.215)**	**<0.001**
2020-2023	**0.110 (0.050-0.242)**	**<0.001**
Age of diagnosis	**0.960 (0.944-0.975)**	**<0.001**

Gender		
Male	Reference	Reference
Female	0,865 (0.462-1.622)	0.651
HIV transmission route		
Heterosexual	Reference	Reference
Homosexual	**0.565 (0,324-0,985)**	**0,044**
Bisexual	1.148 (0.587-2.245)	0.686
Other	1.374 (0.739-2.556)	0.315
Smoking		
Non-smoker	Reference	Reference
Smoker	**0.422 (0.195-0.913)**	**0.028**
Ex-smoker	**0.179 (0.078-0.411)**	**<0.001**
Excessive use of alcohol	1.000 (0.534-1.871)	1.000
Antiretroviral therapy	**0.294 (0.165-0.524)**	**<0.001**
Baseline CD4 count	**0.997 (0.995-0.998)**	**<0.001**
Baseline HIVRNA count	1.000 (1.000-1.000)	0.075
AIDS defining disease	**30.906 (16.302-58.529)**	**<0.001**
Comorbid diseases		
Diabetes mellitus	**0.214 (0.098-0,469)**	**<0.001**
Cardiovascular disease	**0.269 (0.135-0.533)**	**<0.001**
Chronic kidney disease	**0.170 (0.068-0.427)**	**<0.001**
Hypertension	**0.269 (0.144-0.503)**	**<0.001**

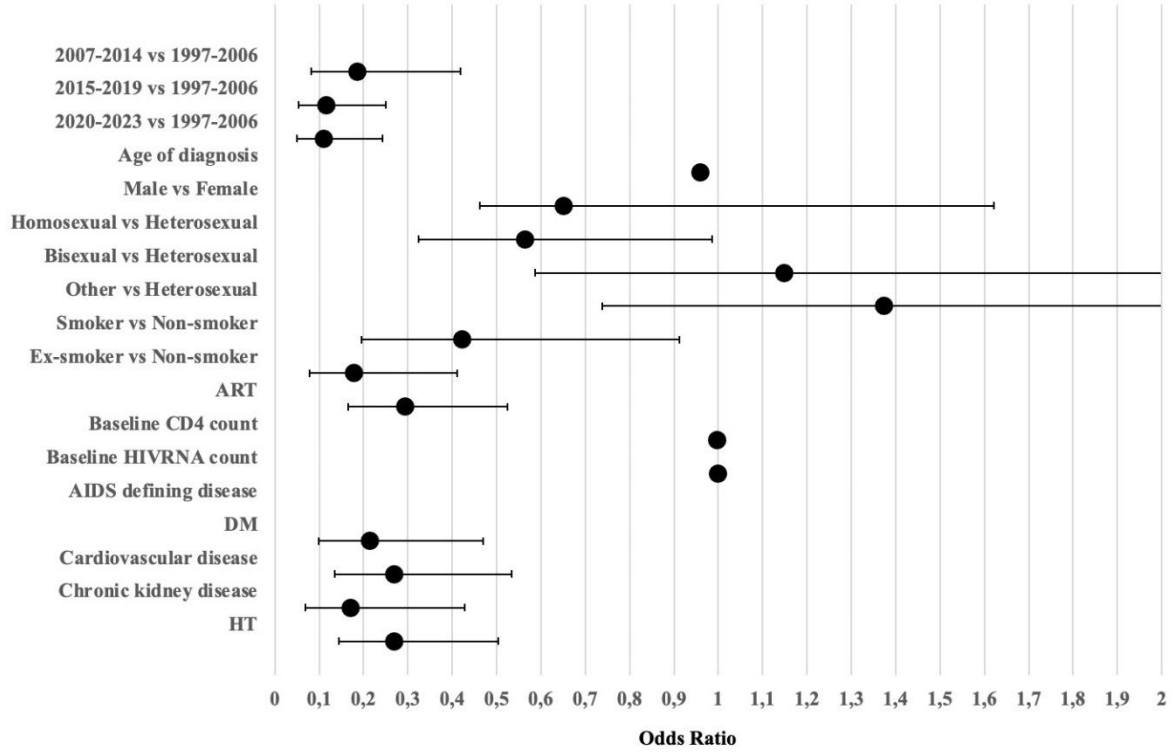


Fig. 1 Forest Plot. Risk factors affecting AIDS-related deaths

Discussion

In this large Turkish cohort of PWH followed between 1997 and 2023, we observed a crude mortality rate of 4.4%. However, this may be an underestimation, as some deceased people may have been lost to follow-up. Studies reported from African countries have also shown that mortality rates based on clinical data are lower than actual mortality rates [8, 9]. It has been decreasing over the years [13]. Mortality rates vary by region, ranging from 5.9% to 8.9% in Japan, Europe, and North America [10, 12, 13], and from 9% to 12.5% in Africa [9, 11]. Notably, mortality has been decreasing over the years [14].

Although life expectancy has increased, our cohort's median age at death was 47 years, almost similar to the European and North American cohorts [10] but much higher than in Africa [9]. The significant increase in the age of death reflects the trend toward non-AIDS-related deaths over time, owing to the broader availability of ART and novel antiretroviral drugs with high efficacy.

Over the years, the proportion of men who have sex with men (MSM) among PWH in our country has increased [15, 16]. Consequently, the proportion of MSM among those who have died has also risen from 7.5% in 1997–2006 to 17.2% in 2020–2023. A similar trend has been reported from the Swiss cohort [10].

Despite all interventions to scale up testing, late diagnosis remains a major problem across Europe and in Türkiye, with rates exceeding 50% [17]. Our study showed that deceased patients had lower CD4 counts, and almost 70% of the deaths occurred in individuals who had an AIDS-defining illness at the time of diagnosis, indicating that HIV was diagnosed late in these cases. As a result, nearly half of the deaths occurred within one

year of HIV diagnosis. Although the number of PLWs with tuberculosis decreased over time, tuberculosis remained the leading cause of AIDS-related deaths in our cohort. HIV and tuberculosis form a deadly combination, accelerating each other's progression [18], and tuberculosis remains a significant public health concern, particularly among PWH in most low-income countries [11, 19].

Although AIDS-related mortality in our cohort has declined over the years, as reported from other studies [10, 14], more than half of the deaths were caused by AIDS-related illnesses. It is also the leading cause of death in HIV cohorts across Europe and North America, but at a much lower rate compared to our cohort. In these regions, AIDS-related mortality significantly declined from 49% in 1996–1999 to 16% in 2016–2020 [10]. In Swiss and French cohorts, AIDS-related deaths ranked third among all causes of death [4, 20]. The risk of HIV/AIDS-related mortality is significantly associated with the country's income level and health policies and may change over time [6]. Since most of these AIDS-related deaths result from severe immune suppression, they can largely be prevented through early diagnosis and treatment of HIV infection.

In our series, infections accounted for a significant proportion of deaths. While the fatality rate from opportunistic infections, particularly tuberculosis, declined over the years, deaths from non-AIDS-related infections increased. Consistent with this trend, the last recorded CD4 count before death was found to be higher over time. These findings suggest a decline in mortality due to opportunistic infections over the years [21, 22].

AIDS-related death was significantly associated with having an AIDS-defining disease at baseline. Patients who died of AIDS-related illnesses were diagnosed at an advanced stage of the disease. The rate of AIDS-related deaths was higher between 1997 and 2006 than in later periods, likely due to the increased use of ART and higher baseline CD4 counts in subsequent years.

In multivariate analysis, we found that AIDS-related deaths decreased with increasing age. This result may be attributed to the increasing prevalence of conditions such as diabetes mellitus and cardiovascular disease with aging, which contribute to overall mortality. AIDS-related deaths were less common among individuals with comorbid conditions like diabetes mellitus, chronic cardiovascular disease, chronic renal failure, and hypertension, as these conditions became more significant causes of death than AIDS in PWH by accelerating the tissue and organ damage. Additionally, the AIDS-related death rate was lower among smokers and ex-smokers, possibly because they were more likely to die from non-AIDS-related diseases due to the damaging effects of smoking. AIDS-related deaths were also less common among MSM than heterosexual men in our series. However, in the early years, when mortality rates were high, the number of reported cases among MSM appeared low because many avoided disclosing their sexual orientation openly. Data from other countries showed a different pattern: Switzerland reported higher mortality rates among MSM, while in England, rates were similar between MSM and heterosexual men [20, 23].

Türkiye is among the countries with a high risk of cardiovascular disease [24]. Deaths from cardiovascular disease have remained stable over the years in our study, similar to the results in other studies [14, 20]. In contrast, cardiovascular-related mortality has decreased in HIV cohorts from Europe and North America. The authors suggest this reduction may be due to improvements in post-cardiovascular disease care and possibly the reduced toxicity of ART regimens used in recent years [10].

The most common cause of death among individuals living with HIV was cancer, accounting for almost a third of deaths. The proportion of AIDS-related cancers (15.9%) has remained relatively stable over time, whereas non-AIDS-related cancers (11.6%) have increased. The analysis of the solid organ cancers (39 deaths) subgroup revealed that they showed an increasing trend over the years, with the most common being lung cancer. Suarez-Garcia et al. reported that lung and liver cancers were the most frequent non-AIDS-related causes of death [25]. A similar trend was observed in a study conducted in China [26]. Weber and colleagues noted an increase in lung cancer deaths over time, while liver-related causes, including hepatic cancers, have decreased. They identified an association between heavy smoking and the increased risk of lung cancer death [20]. The high percentage of current and ex-smokers in our cohort may be a major contributor to the high rate of lung cancers. On the other hand, due to the low prevalence of chronic hepatitis B and the very low prevalence of hepatitis C, deaths due to liver cancer remained extremely low in contrast to the reports mentioned above.

In this study, six deaths (1.4%) were attributed to suicide. According to the Turkish Statistical Institute, suicide accounted for 0.77% of all deaths in Türkiye in 2023 [27]. In other countries, suicide-related deaths among PWL have been reported at rates 3.2–12.5% higher than ours [12, 13, 20, 28]. However, it is possible that we were unable to capture data on some patients who died by suicide. The higher proportion of suicide-related deaths among PWL compared to the general population has also been reported in other studies [12, 28]. These findings highlight the need for targeted mental health interventions and suicide prevention strategies within HIV care programs.

This study has several limitations. First, as a retrospective study, it is subject to potential unmeasured confounding. Second, we assessed mortality only as a crude rate and may have missed some deaths due to loss of follow-up. Third, we could not determine the annual mortality rate or identify risk factors for mortality, as the analysis did not include data from surviving patients.

In Türkiye, prospective cohort studies are needed to determine the annual incidence of HIV-related deaths and identify the risk factors associated with mortality. These studies would provide crucial data to help improve healthcare responses and tailor interventions to reduce mortality rates among people living with HIV.

In conclusion, more than half of the deaths among our patients were caused by AIDS-related illnesses, which are largely preventable through early diagnosis and treatment of HIV infection. Overall, AIDS-related deaths have declined over time, while the proportion of deaths due to non-AIDS-related cancers has increased, and the mortality rate from cardiovascular disease has remained unchanged. This study is one of the few studies reporting on causes of death in Türkiye. It has significant limitations, such as a lack of data on annual mortality rates and risk factors for mortality. As most of the deaths are preventable, it is of utmost importance to collect and analyze the required data that would represent the Turkish PWH population to develop relevant interventions to address preventable factors of death and to reduce premature deaths.

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