# Causes of death and mortality trends of all individuals reported with HIV/AIDS in Israel, 1985–2010

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**ABSTRACT**

**Background** Highly active antiretroviral therapy (HAART) has changed life-expectancy and mortality trends among people living with HIV/AIDS (PLWHA) since 1996. This retrospective cohort study aimed to assess the mortality epidemiology of PLWHA in Israel and analyze the causes of death.

**Methods** This cohort study included all adult Israeli-citizens PLWHA between 1985 and 2010 and crossed matched with the Civil Registry to identify those who died. Death certificates were classified into AIDS or non-AIDS deaths related-causes. Standardized mortality-ratio (SMR) represented mortality excess.

**Results** Of all 5140 PLWHA who were followed-up for 36 955 person-years, 1066 (20.7%) died. The ratio of AIDS-related deaths to non-AIDS related deaths reduced from 1.2:1 before 1996 to 0.6:1 after 1997, and case-fatality rates reduced from 12.0 to 0.9%, respectively ($P < 0.001$). SMR were 3.0 (95% CI: 2.3–3.5) for males and 3.9 (95% CI: 3.3–4.5) for females.

Fatality cases were more likely older Israeli-born males, co-infected with tuberculosis, reported before 1996 and acquired HIV by drug-injection or infected-blood products. Deaths of AIDS-related causes were common among Israeli-born gay men, while non-AIDS deaths were common among those reported after 1997 and drug users.

**Conclusions** Death rates declined since HAART introduction. Yet, SMR remained high, and PLWHA infected by drug-use or blood-products have not enjoyed relative longevity.

**Keywords** AIDS, death, HIV, Israel, mortality, risk groups

## Introduction

Life expectancy of people living with HIV/AIDS (PLWHA) has increased considerably since the introduction of the highly active antiretroviral therapy (HAART) in the mid-1990s due to the reconstitution of immune response. HIV/AIDS has gradually been considered as a chronic disease with life expectancy almost comparable to non-HIV chronic illnesses.[1] This evolving scenario signals a profound change in epidemiology approach to the HIV epidemic. The risk factors for the post-HAART morbidity and mortality are currently multifactorial, and include long-term immunodeficiency and viraemia, HAART toxicity, aging and unhealthy lifestyle.[2] Subsequently, AIDS-related deaths among PLWHA in developed countries have decreased, with an increase in the non-AIDS related cause of deaths.[3–8] These include non-AIDS related malignancies and infections, as well as cardiovascular, hepatic and renal diseases.[9]

Israel is a developed country with a gross domestic product of $29 800[10] per person, including nearly 7.7 million citizens, of whom nearly 2.5 million (~32%)[11] are non-Israeli born, and about 200 000 (~2.5%) are non-citizen migrants who arrived in Israel mostly for labor purposes.[12] From 1981 to 2010, 6579 HIV/AIDS cases were reported nationally, in an upward trend from 3.6 new HIV-diagnoses per 100 000 population in 1986 to 5.6 in 2010. Immigrants from countries of generalized epidemic (ICGE) comprised 2717

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(41.3%) of all cases. Of those, 2089 (76.9%) were Israeli citizens and 628 (23%) were non-citizens migrants, mostly migrant workers. The majority ($N = 2040$) of ICGE Israeli citizens were born in Ethiopia.[13]

This cohort study aims, for the first time in Israel, to assess mortality trends among PLWHA for a 25-year period, analyze the relevant causes of death and compare their mortality rates and reason of death with that of the general Israeli population. Valid data regarding the causes of death of PLWHA may guide treating physicians to prioritize care for PLWHA, and promote appropriate medical infrastructure for potential change in morbidity and mortality trends.

## Methods

### Data collection and definitions

This retrospective cohort study included all PLWHA in Israel who were citizens older than 16 years of age and diagnosed between January 1985 and December 2010. HIV/AIDS is a mandatory reportable disease and the completeness of notification in Israel is estimated to be at 100%, as notification is a perquisite for medical follow-up and treatment.[13] Identifiable notifications are sent from the reporting physicians or laboratories to the regional health, and then to the National level.

PLWHA who are Israeli citizens are treated in one of the eight AIDS-centers and are covered by the National health insurance. HAART has been fully available in Israel for no charge since 1997 for PLWHA, according to clinical and laboratory criteria. Drug initiation and regimen are regularly updated according to international guidelines.

Data regarding PLWHA were collected from National HIV/AIDS Registry (NHAR) in the Ministry of Health. This registry receives reports from the AIDS treatment centers, health funds and health departments country-wide.[13] These reports contain demographic (name, ID number, family status, address, country of birth and citizenship), behavioral and clinical data for each notification. Behavioral data include the route of HIV infection as were reported by the patients: intravenous drug users (IVDU) or infected from blood products, men who have sex with men (MSM), heterosexuals and those of unknown risk behavior. In response to a possible reporting bias of newly diagnosed patients who may refrain from disclosing their risk behavior upon diagnosis, the NHAR is periodically updated with continuous name-based reports from all the AIDS treatment centers and the regional health departments regarding behavioral and clinical changes.[13] In addition, the NHAR is crossed matched bi-annually with data from all four medical insurers to update the NHAR regarding HAART initiation for each person.

As the National Civil Registry captures only Israeli citizens, only PLWHA citizens were included in this study. All PLWHA, who were Israeli citizens registered in the NHAR, were crossed matched with the National Civil Registry in January 2011 by their names and identification numbers to identify those who died or left Israel.

All death certificates and the final hospitalization records of deceased PLWHA were collected from the relevant health departments, hospitals and the death registry at the Ministry of Health. Causes of death were recorded retrospectively by an experienced death registrar and experienced AIDS epidemiologists independently. In case of inconsistency, a third AIDS treating physician was consulted. The underlying cause of death was defined as the disease or injury which initiated the train of morbid events leading directly to death by the rules of the International Classification of Diseases, ninth Revision, Clinical Modification (ICD-9-CM).[14] The causes of death were categorized into AIDS-related deaths, which included the Centers for Disease Control and Prevention classification to AIDS-defining infections and AIDS-defining malignancies;[15] and also to non-AIDS-related deaths, and included all other underlying causes of death, which were further sub-divided by non-AIDS causes.[6]

### Statistical analysis

The follow-up time started at the date of HIV/AIDS reporting and terminated on the date of death, leaving Israel or December 2011 (whatever came first), and was determined by person-years (PY). Case fatality rate (CFR) was calculated as the annual number of AIDS and non-AIDS related deaths divided by the prevalent number of PLWHA each year. Trend analysis was performed by the Chi-square test to yield the linear-by-linear association test. Comparisons between PLWHA who were Israeli citizens and died with that of PLWHA who survived were performed by the Chi-square test for categorical variables, while continuous variables were compared by the Student's $t$-test for variables distributed normally. Characteristics which achieved $P < 0.05$ were considered statistically significant and included in the multivariable Cox proportional hazard models after assessing for collinearity to evaluate the association of specific independent factors predicted mortality, which were expressed as hazard-ratios and 95% confidence intervals (95% CI). Comparisons between PLWHA who died of AIDS-related causes to those died of non-AIDS related causes were performed by logistic regression for variables achieved statistically significant values in the univariate analysis and following assessment of collinearity.

Kaplan–Meier and Cox regression plots of PLWHA were outlined to describe survival time in years by risk group of HIV-transmission.

Excess in mortality among PLWHA was evaluated on the basis of standardized mortality ratio (SMR) by the indirect age adjustment to observed number of PLWHA-citizens who died divided by the expected number of deaths in the relevant age-group and gender of the general population of Israel in 2005, as published by the Central Bureau of Statistics[16] with 95% CI.

Years of potential life lost (YPLL) were calculated as the sum of years lost because of premature death. Abridged life Tables were constructed from age specific mortality from this cohort and compared to the gender and age specific life expectancy rates in Israel.

All analyses were performed by the SPSS® program version 19.0. The study was approved by the Ben Gurion University Institutional Review Board (#2010–8).

## Results

This study, which comprised of 36 955 PY of all 5140 PLWHA who were Israeli citizens older than 16 years of age and followed-up for 25 years, found that 1066 (20.7%) have died during the follow-up period (2.6 deaths per 100 PY). While the number of annual new HIV/AIDS notifications has increased throughout the study period, the annual rates of death among PLWHA have been reduced from 100 to 1.2% (trend analysis $P < 0.001$, Fig. 1a). Concomitantly, the average ratio of AIDS-related deaths to non-AIDS related deaths has reduced from 1.2:1 before 1996 to 0.6:1 after 1997 and CFR had reduced from 12.0 to 0.9% during the same time (trend analysis $P < 0.001$, Fig. 1b).

Average age adjusted SMR were 3.0 (95% CI: 2.3–3.5) for males and 3.9 (95% CI: 3.3–4.5) for females. YPLL among males who were diagnosed before 1996 were 21 157 and 4483 for those diagnosed after 1997, while among females were 12 903 and 5035, respectively.

PLWHA who were males, older, Jews, Israeli born, co-infected with tuberculosis, diagnosed before 1996 and IVDU or infected from blood products were more likely to die than PLWHA who survived by the end of the study follow-up (Table 1). Interestingly, PLWHA diagnosed before 1996 and died were more likely to be Israeli-born and MSM, while this trend has been overturned after 1997. Since then, and following the introduction of the HAART, PLWHA who were diagnosed and died were more commonly non-Israeli born, and MSM were less likely to die. In the multivariate analysis, being male, older, born in Israel, co-infected with tuberculosis, reported with HIV before 1996, acquiring the HIV by IVDU or infected blood products predicted death. Being born in Israel and MSM were variables predicting death before 1996, but not after 1997 (Table 2).

Death rates varied by key risk groups of HIV infections. PLWHA who were infected by blood products or IVDU were more likely to die than MSM or heterosexuals, both before 1996 (Fig. 2a) or after 1997 (Fig. 2b). MSM who were diagnosed after 1997 were more likely to survive than heterosexuals.

All mortality cases were divided between those who died of AIDS-related causes and non-AIDS related causes. AIDS-related deaths were more common among older, Israeli-born and MSM and those whose cause for HIV transmission was unknown, while IVDU were less likely to die of AIDS-related causes (Table 3). Non-AIDS related deaths were common among older males, those who were co-infected with tuberculosis, reported after 1997 and attributed to IVDU or unknown causes than those died of AIDS-related causes. Variables predicted AIDS-related deaths in multivariate analysis included being older, Israeli-born, MSM and those with unknown route of HIV-transmission. Variables predicted non-AIDS related deaths in multivariate analysis included being male, older, co-infected with TB, reported after 1997 and IVDU.

In comparison of those who died before the introduction of HARRT in 1996 to those who died after its introduction in 1997, it was found that those who died in the later period were less likely to die of AIDS-related cancers, but more likely to die of non-AIDS related cancers than those diagnosed before 1996 (Table 4). Additionally, those who died after HAART introduction were less likely to die of general deterioration and pulmonary causes than those who died prior to HAART, but more likely to die of external reasons and overdose, as well as from mortality related to liver/pancreas, CVA/brain, cardiac and kidney causes.

## Discussion

### Main findings of this study

The overall mortality rates in this nationwide study have been reduced significantly during the study period. Nevertheless, PLWHA remained at higher risk of death compared to the general population. The reduction in mortality rate following the introduction of HAART in 1997 has also reflected the causes of death, changing from AIDS-related deaths which were more common before 1996, to the currently non-AIDS related deaths. Death among PLWHA has become more prevalent among older Israeli-born males who acquired HIV by IVDU or infected blood products.

### What this study adds

PLWHA who were diagnosed before 1996 were not treated with HAART. Even thereafter, during the early years
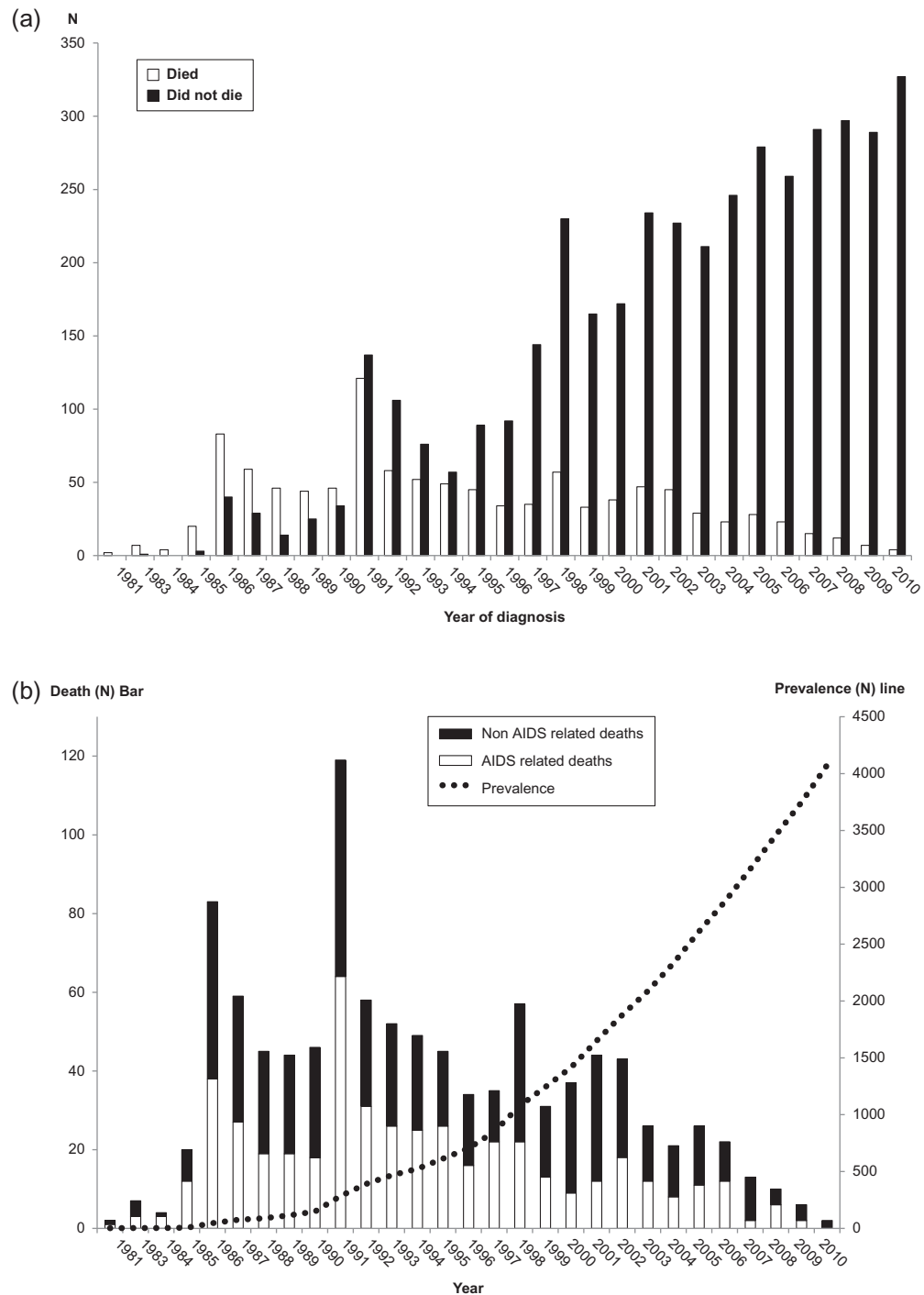
**Fig. 1** (**a**) Number of new notification and deaths reported annually among adult Israeli citizens infected with HIV, 1985–2010. (**b**) Causes of death and case fatality rate of adult Israeli citizens infected with HIV in Israel, 1985–2010.

following its introduction, patients were prescribed HAART to treat more advanced conditions, and received regimens that were inferior to the currently prescribed drugs in terms of viral suppression, pill burden, toxicity and serious adverse events. Modern first line regimens are currently more robust

than earlier therapy, and adherence has been improved by once daily treatment, all of which contribute to better virological control and, ultimately, greater life expectancy.[17]

However, PLWHA are now reaching ages at which non-AIDS causes of death, such as cancer and heart disease, are

**Table 1** Characteristics of all 5140 people infected with HIV in Israel, divided to those who died or survived, by time of reporting, 1981–2010

| | | All | | | | | Reported before 1996 | | | | | Reported after 1997 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Died | Did not die | PY | Rate per 1000 PY | P | Died | Did not die | PY | Rate per 1000 PY | P | Died | Did not die | PY | Rate per 1000 PY | P |
| Sex | Male | 841 (78.9) | 2635 (64.7) | 24 006 | 35.0 | <0.01 | 532 (83.6) | 198 (65.2) | 13 845 | 3.8 | <0.01 | 309 (71.9) | 2237 (64.4) | 13 741 | 22.5 | 0.003 |
| | Female | 225 (21.1) | 1438 (35.3) | 12 949 | 17.4 | | 104 (16.4) | 212 (34.8) | 10 265 | 10.1 | | 121 (28.1) | 1226 (35.6) | 8565 | 14.1 | |
| Age (years, average ± SD) | | 38.3 ± 13.4 | 34.3 ± 10.7 | | | <0.01 | 56.1 ± 12.5 | 48.7 ± 10.8 | | | <0.01 | 51.2 ± 14.6 | 41.6 ± 11.1 | | | <0.01 |
| Religion | Jews | 947 (88.8) | 3071 (75.4) | 31 116 | 30.4 | <0.01 | 586 (92.1) | 550 (90.0) | 13 295 | 44.1 | 0.1 | 361 (84.0) | 2521 (72.8) | 17 821 | 20.3 | <0.01 |
| | Non-Jews | 119 (11.2) | 1003 (24.6) | 5860 | 20.3 | | 50 (7.9) | 61 (10.0) | 1375 | 36.4 | | 69 (16.0) | 942 (27.2) | 4485 | 15.4 | |
| Country of birth | Israeli born | 364 (34.1) | 1150 (28.2) | 9580 | 38.0 | <0.01 | 283 (44.5) | 162 (26.5) | 4617 | 61.3 | <0.01 | 81 (18.8) | 988 (28.5) | 4964 | 16.3 | <0.01 |
| | Non-Israeli born | 702 (65.9) | 2924 (71.8) | 27 395 | 25.6 | | 353 (55.5) | 449 (73.5) | 10 052 | 35.1 | | 2475 (71.5) | 349 (81.2) | 17 344 | 142.7 | |
| TB | TB infected | 130 (12.2) | 188 (4.6) | 2780 | 46.8 | <0.01 | 74 (11.6) | 47 (7.7) | 1410 | 52.5 | 0.02 | 56 (13.0) | 141 (4.1) | 1370 | 40.9 | <0.01 |
| | No TB infection | 936 (87.8) | 3886 (95.4) | 34 195 | 27.4 | | 562 (88.4) | 564 (92.3) | 13 259 | 42.4 | | 374 (87.0) | 3322 (95.9) | 20 936 | 158.7 | |
| Period of HIV reporting | Before 1996 | 636 (59.7) | 611 (15.0) | 14 669 | 43.4 | <0.01 | | | | | | | | | | |
| | After 1997 | 430 (40.3) | 3463 (85.0) | 22 306 | 19.3 | | | | | | | | | | | |
| Risk group | MSM | 220 (20.3) | 1080 (26.1) | 7376 | 29.8 | <0.01 | 179 (28.1) | 132 (21.6) | 3263 | 54.9 | <0.01 | 41 (9.56) | 948 (27.4) | 4113 | 10.0 | <0.01 |
| | IVDU | 247 (22.8) | 611 (15.0) | 5660 | 43.6 | | 125 (19.7) | 59 (8.7) | 1837 | 68.0 | | 122 (28.4) | 552 (15.9) | 3858 | 31.6 | |
| | Blood | 77 (6.7) | 18 (0.4) | 805 | 95.7 | | 66 (10.4) | 15 (2.5) | 777 | 84.9 | | 5 (1.2) | 3 (0.1) | 30 | 166.7 | |
| | Unknown | 56 (5.3) | 50 (1.2) | 704 | 79.5 | | 27 (4.2) | 19 (3.1) | 470 | 57.4 | | 25 (6.3) | 29 (0.9) | 244 | 102.5 | |
| | Hetero | 472 (44.3) | 2315 (56.8) | 22 385 | 21.1 | | 239 (37.6) | 386 (63.2) | 8321 | 28.7 | | 233 (54.2) | 1929 (55.7) | 14 063 | 16.6 | |

SD, standard deviation; TB, tuberculosis.

**Table 2** Multivariate analysis of variables predicting death among adult Israeli citizens infected with HIV in Israel, by time of reporting

| Characteristic | All deaths | Deaths of those reported before 1996 | Deaths of those reported after 1997 |
| --- | --- | --- | --- |
| | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Male | 1.3 (1.1–1.5) | 1.2 (1.1–1.3) | 1.3 (1.1–1.6) |
| Age (5 years interval) | 1.2 (1.2–1.3) | 1.3 (1.1–1.7) | 1.3 (1.2–1.5) |
| Israeli born | 1.3 (1.1–1.6) | 1.6 (1.3–1.9) | 1.1 (0.8–1.5) |
| Tuberculosis co-infection | 1.9 (1.6–2.4) | 1.9 (1.5–2.5) | 2.2 (1.6–2.9) |
| Reported before 1996 | 2.9 (2.6–3.3) | | |
| MSM | 1.1 (0.9–1.4) | 1.5 (1.2–2.0) | 0.6 (0.4–0.8) |
| IVDU | 2.4 (2.0–2.8) | 2.2 (1.7–2.8) | 2.4 (1.9–3.1) |
| Infected from blood products | 2.2 (1.8–3.2) | 2.3 (1.7–3.1) | 5.7 (2.3–6.8) |
| Unknown risk group | 2.7 (2.0–3.6) | 1.7 (1.2–2.7) | 5.8 (3.8–8.7) |

OR, odds ratio.



(a)

increasingly common. An increase in non-AIDS related deaths has been recorded since 1997, which could be related to several major causes, including adverse events associated with the HAART, prolonged life expectancy or lifestyle factors.

First, the impact of HAART on blood vessels and lipid distribution, and particularly the medications which include protease inhibitors, could have contributed to the development of metabolic dysfunction and altered cholesterol and lipids leading to a more atherogenis profile.[18] This may explain the elevated risk related to vascular diseases recorded after 1997, such as CVA or cardiac diseases compared with the period before HARRT were available.

Second, prolonged life expectancy, the major advantage of the HAART, has contributed to the aging of PLWHA. Comorbid conditions have become more instrumental in morbidity and mortality of PLWHA who are in clinical care. Complications of aging among PLWHA are becoming more prevalent, such as non-AIDS related cancers, especially lung cancer, osteoporosis and cardiovascular diseases.[19]

Third, lifestyle factors, such as smoking, drug misuse and alcoholism, which are all higher among people with HIV, can lead to the elevated risk of deaths from cardiovascular disease, cancer, liver disease, pulmonary infections, suicide, overdose and injury.[2,20]

While AIDS-related mortality in the pre-HAART period was substantial, death rate has decreased after 1997. However, external causes of deaths have increased since, and accounted for a significant proportion of mortality among PLWHA, as
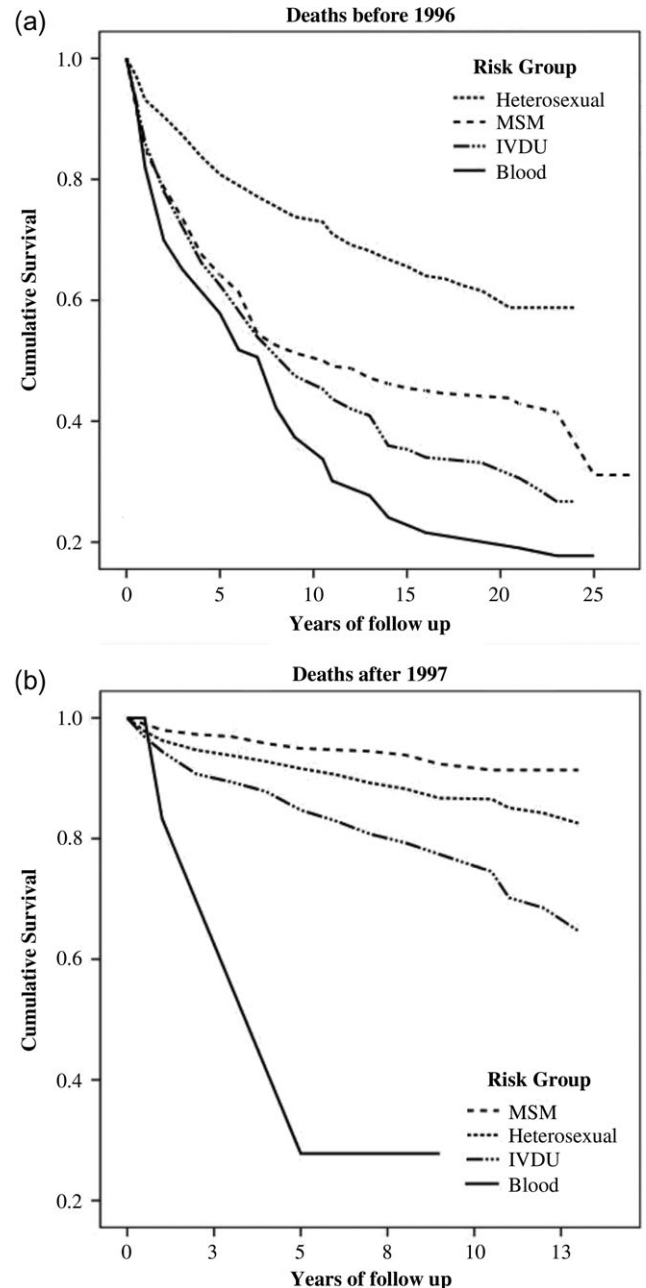


(b)

**Fig. 2** (**a**) Adjusted Cox proportional hazard regression curve comparing AIDS-related deaths among people infected with HIV, by transmission route, 1985–2010. (**b**) Adjusted Cox proportional hazard regression curve comparing non-AIDS related deaths among people infected with HIV, by transmission route, 1985–2010.

found in other studies,[3] in addition to mortality due to chronic diseases, which are probably related to aging of the study population and increasing time of exposure to HAART.

IVDU were less likely to demonstrate longer life-expectancy than PLWHA who were infected by other transmission routes. They were more susceptible to external causes of deaths and

**Table 3** Characteristics of all 5140 Israeli citizens infected with HIV in Israel, by reason of death, divided to those who died and survived, 1981–2010

| | | AIDS related deaths | | | | | Non-AIDS related deaths | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Died | Did not die | OR^ (95% CI) | P | Adjusted OR (95% CI) | Died | Did not die | OR^ (95% CI) | P | Adjusted OR (95% CI) |
| Sex | Male | 366 (76.7) | 3110 (66.7) | 0.9 (0.7–1.1) | <0.01 | 0.8 (0.6–1.1) | 460 (81.7) | 3016 (65.9) | 1.2 (1.1–1.5) | <0.01 | 1.3 (1.1–1.6) |
| | Female | 111 (23.3) | 1552 (33.3) | 1 | | 1 | 103 (18.3) | 1560 (34.1) | 1 | | 1 |
| Age (years, average ± SD) | | 38.6 ± 14.1 | 34.8 ± 11.1 | 1.1[a] (1.0–1.2) | <0.01 | 1.1 (1.1–1.2) | 38.1 ± 12.8 | 34.8 ± 11.2 | 1.1[a] (1.0–1.2) | <0.01 | 1.1 (1.1–1.2) |
| Religion | Jews | 429 (89.9) | 3589 (77.0) | 0.8 (0.6–1.1) | <0.01 | | 498 (88.5) | 3520 (76.9) | 0.6 (0.5–0.8) | <0.01 | |
| | Non-Jews | 48 (10.1) | 1074 (23.0) | 1 | | | 65 (11.5) | 1057 (23.1) | 1 | | |
| Country of birth | Israeli born | 164 (34.4) | 1350 (29.0) | 1.2 (1.1–1.4) | 0.01 | 1.1 (0.8–1.3) | 195 (14.6) | 1319 (28.8) | 1.1 (0.9–1.3) | <0.01 | |
| | Non-Israeli born | 313 (65.6) | 313 (71.0) | 11 | | | 368 (65.4) | 3258 (71.2) | 1 | | |
| TB | TB infected | 84 (17.6) | 234 (5.0) | 1.1 (0.9–1.4) | <0.01 | | 43 (7.6) | 275 (6.0) | 1.5 (1.2–1.8) | 0.1 | 1.2 (1.1–1.7) |
| | No TB infection | 393 (82.4) | 4429 (95.0) | 1 | | | 520 (92.4) | 4302 (94.0) | 1 | | 1 |
| Period of HIV reporting | Before 1996 | 312 (65.4) | 935 (20.1) | 1 | <0.01 | | 321 (57.0) | 926 (20.2) | 1 | <0.01 | 1 |
| | After 1997 | 165 (34.6) | 3728 (79.9) | 1.2 (0.8–1.9) | | | 242 (43.0) | 3651 (79.8) | 1.8 (1.3–2.1) | | 1.5 (1.4–1.8) |
| Risk group | MSM | 117 (24.5) | 1183 (25.4) | 1.4 (1.1–1.9) | <0.01 | 1.4 (1.1–1.8) | 99 (17.6) | 1201 (26.2) | 1.1 (0.9–1.5) | <0.01 | 1.2 (1.1–1.6) |
| | IVDU | 63 (13.2) | 795 (17.0) | 0.6 (0.5–0.8) | | 0.6 (0.5–0.8) | 174 (30.9) | 684 (14.9) | 1.8 (1.4–2.2) | | 0.7 (0.4–1.1) |
| | Blood | 37 (7.8) | 52 (1.1) | 1.0 (0.7–1.4) | | 0.9 (0.6–1.3) | 34 (6.0) | 55 (1.2) | 0.8 (0.6–1.2) | | 1.9 (1.2–2.9) |
| | Unknown | 23 (4.8) | 83 (1.8) | 1.6 (1.1–2.4) | | 1.6 (1.1–2.4) | 33 (5.9) | 73 (1.6) | 2.4 (1.7–3.5) | | 1.2 (1.1–1.6) |
| | Hetero | 237 (49.7) | 2550 (54.7) | 1 | | 1 | 223 (39.6) | 2564 (56.0) | 1 | | 1 |

SD, standard deviation; TB, tuberculosis.

[a] 5 Years interval.

**Table 4** Reasons of death of Israeli citizens infected with HIV, by time of death, 1985–2010

| Reason | Died before 1996 | Died after 1997 |
|---|---|---|
| AIDS related | | |
| Infections | 266 (42.0) | 135 (33.2) |
| Cancer | 43 (6.8) | 30 (7.4) |
| Wasting or general deterioration | 3 (0.5) | 0 (0) |
| Non-AIDS related | | |
| Infections | 35 (5.5) | 24 (5.9) |
| Cancer | 16 (2.5) | 25 (6.1) |
| Wasting or general deterioration | 68 (10.7) | 23 (5.7) |
| External reasons | 30 (4.7) | 26 (6.4) |
| Pulmonary | 15 (2.4) | 11 (2.7) |
| Overdose | 9 (1.4) | 20 (4.9) |
| Liver/pancreas | 29 (4.6) | 31 (7.6) |
| CVA/brain | 7 (1.1) | 11 (2.7) |
| Cardiac | 3 (0.5) | 13 (3.2) |
| Kidney | 6 (0.9) | 7 (1.7) |
| Unknown | 103 (16.3) | 51 (12.5) |

homicide due to the risk pertaining to illegality of drug-trade, and also due to overdose. Additionally, their personal characteristics, environmental exposures, and inferior basic health conditions—all exposed them to further harm. Lastly, their possible HIV-late diagnosis and the limited adherence to HAART once recommended have probably led to the excess in mortality.[3,21–23]

PLWHA who were infected by blood transfusion were also less likely to enjoy longevity. Blood transfusion was the main route of HIV-infection in the early phase of AIDS in Israel, and most were diagnosed before 1985. Their relatively older age, longer exposure to HIV and HAART may have contributed to their higher mortality rate.

On the other hand, being MSM was found a protective factor in this study. Their relatively younger age,[13] early HIV-diagnosis and their high adherence to medical follow-up and HAART most probably contributed to their well-being and decreased morbidity and mortality.[3]

The lower death rates among female PLWHA compared to males could be explained by a possible early HIV-diagnosis through screening in antenatal clinics, resulting in women receiving treatment at a high CD4 count. It may also stem from life-style differences that were exaggerated in male patients (e.g. smoking, alcohol and drug misuse).[17]

While the rate of AIDS-related cancer mortality has been stable after the introduction of the HAART, the rate of death due to non-AIDS related cancer has increased, in line

with other studies.[6] Another publication found that of all PLWHA in Israel who had been followed-up for a similar period to this current cohort, 362 (7.0%) developed cancer (~1 case per 100 PY), higher in the pre-ART period than after 1997 (1.2 and 0.85 cases per 100 PY, respectively).[24] Higher hazard-ratios to develop cancer were demonstrated among older PLWHA, Jews, and IVDU. It may be that advanced age and greater cumulative exposure to environmental (such as tobacco and alcohol) or viral (Human Herpes Virus-8, Human Papilloma Virus, hepatitis B or Epstein Barr viruses) carcinogens are associated with the increased risk of malignancies.[25]

## Limitations of this study

This study was based on the high quality NHAR, which included all PLWHA registered in Israel and crossed matched with the Israeli Civil Registration for a long observation period, and therefore generalizable. However, the results of this study should be interpreted in light of several limitations. First, the sources for mortality data were mostly death certificates. The challenge to determine the underlying cause of death may be subject to the knowledge of the physician who signed the death certificate or to the understanding of the evaluating researcher, as several diseases and risk factors may contribute in the train of events leading to death. Additionally, contributory causes of death may have been incomplete if the physician who signed the death certificate was unfamiliar with the patient's full medical history. In order to reduce this information bias, those whose death certificates or hospitalization records were not clear were classified as 'unknown'. The second limitation is the cohort effect—meaning different exposures and risks throughout the study period. This limitation was ameliorated by comparing the period before and after HAART introduction and using Kaplan Meier designs. Third, CD4 counts and the exact date of HAART initiation were not available to evaluate its impact on survival. Fourth, this study did not capture individualized life-style factors that could be associated with late treatment or life expectancy.

In summary, our findings contribute to the growing number of publications demonstrating a decline in deaths among PLWHA and a shift to increasing proportions of deaths due to non-AIDS causes. Additionally, this study has described that IVDU and those infected by blood transfusion were less likely to gain the benefits of the HAART and the improvement in life expectancy was not as long as those infected by other routes. As the prevalence and age of the PLWHA in Israel continues to increase, the findings from this study highlight the importance of adherence to treatment regimens, and established guidelines of screening of non-AIDS cancers[26] and hepatitis[27] among PLWHA. Additionally, PLWHA may benefit

from primary prevention programs to prevent or eliminate the exposure of tobacco and other substances.

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