

Survival of Persons with and without HIV Infection in Denmark, 1995–2005

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Background: The expected survival of HIV-infected patients is of major public health interest.

Objective: To estimate survival time and age-specific mortality rates of an HIV-infected population compared with that of the general population.

Design: Population-based cohort study.

Setting: All HIV-infected persons receiving care in Denmark from 1995 to 2005.

Patients: Each member of the nationwide Danish HIV Cohort Study was matched with as many as 99 persons from the general population according to sex, date of birth, and municipality of residence.

Measurements: The authors computed Kaplan–Meier life tables with age as the time scale to estimate survival from age 25 years. Patients with HIV infection and corresponding persons from the general population were observed from the date of the patient's HIV diagnosis until death, emigration, or 1 May 2005.

Results: 3990 HIV-infected patients and 379 872 persons from the general population were included in the study, yielding 22 744 (me-

dian, 5.8 y/person) and 2 689 287 (median, 8.4 years/person) person-years of observation. Three percent of participants were lost to follow-up. From age 25 years, the median survival was 19.9 years (95% CI, 18.5 to 21.3) among patients with HIV infection and 51.1 years (CI, 50.9 to 51.5) among the general population. For HIV-infected patients, survival increased to 32.5 years (CI, 29.4 to 34.7) during the 2000 to 2005 period. In the subgroup that excluded persons with known hepatitis C coinfection (16%), median survival was 38.9 years (CI, 35.4 to 40.1) during this same period. The relative mortality rates for patients with HIV infection compared with those for the general population decreased with increasing age, whereas the excess mortality rate increased with increasing age.

Limitations: The observed mortality rates are assumed to apply beyond the current maximum observation time of 10 years.

Conclusions: The estimated median survival is more than 35 years for a young person diagnosed with HIV infection in the late highly active antiretroviral therapy era. However, an ongoing effort is still needed to further reduce mortality rates for these persons compared with the general population.

Ann Intern Med. 2007;146:87-95.

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Knowing the expected survival of HIV-infected patients is of major public health interest. Mortality rates have decreased substantially in recent years as a result of improved effectiveness of highly active antiretroviral therapy (HAART) (1). Studies comparing mortality rates for HIV-infected persons with age- and sex-specific mortality rates for the general population (2–5) have reported 3- to 10-fold increase in successfully treated patients. The relative mortality rate, however, is highly dependent on the age distribution of the study sample and does not in itself answer questions about survival. We therefore aimed to estimate median survival and age-specific mortality rates for an entire HIV-infected population compared with a cohort from the general population. Persons with HIV infection were followed from before initiation of HAART and included those with such predictors of lower survival as poor response to therapy, AIDS diagnosis, low CD4 count, high viral load, and poor adherence to treatment (6, 7). Linking data from the population-based Danish HIV Cohort Study (DHCS) (8) and the Danish Civil Registration System (CRS) (9, 10) allowed us to use product-limit methods that are analogous to the period life tables used by national authorities for estimating median survival (11).

METHODS

Study Sample

The DHCS is a prospective, nationwide, population-based cohort study of all HIV-infected persons treated in Danish HIV clinics since 1 January 1995 (8, 12). The study is ongoing, with continuous enrollment of both newly diagnosed residents and immigrants with existing HIV infection. Treatment for HIV infection in Denmark is restricted to 8 specialized centers, and the Danish health care system provides free tax-supported medical care, including antiretroviral treatment for HIV infection. The study databases are updated annually. Adult (>16 years) DHCS participants with residency in Denmark were included at their first visit to an HIV clinic. The Civil Registration System (CRS) is a national registry of all Danish

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Context

The expected survival of HIV-infected patients has been difficult to measure by comparing selected HIV samples and control groups.

Contribution

Denmark carefully tracks each of its residents' vital status, which makes it possible to accurately compare survival of HIV-infected persons and uninfected persons. In 2000 to 2005, life expectancy at age 25 years was 51 years in the general population and 39 years for HIV-infected persons without hepatitis C virus infection (HCV).

Cautions

Denmark provides excellent access to HIV and HCV care, so the results may be atypical.

Implications

Persons with HIV infection have a good, but far from normal, life expectancy.

—The Editors

residents; this registry contains information on date of birth; sex; address; date of migration; and date of death, if applicable (9). A 10-digit personal number (Central Person Registry [CPR] number), assigned at birth, uniquely identifies each person. The CRS is updated within a week of a person's birth, address change, death, or emigration. Use of the CPR number enables treatment centers to avoid multiple registrations of the same patient and allows tracking of deaths and persons lost to follow-up due to emigration. Using the CRS records, we drew a random sample of persons from the general population and matched them to each HIV-infected patient according to sex and month of birth and residence in the same municipality as the patient on the date of diagnosis (Denmark has a population of approximately 5.3 million persons living in 270 municipalities). We aimed to sample 99 persons from the general population for each HIV-infected person. However, because of a shortage of eligible persons in some municipalities, the mean number of persons from the general population per patient was 95.2 in the final sample.

Patients with at least 1 positive result on a hepatitis C virus (HCV)–antibody test or a positive result on an HCV RNA test were considered to be HCV-positive; the other patients were considered to be HCV-negative. The HCV-antibody status was available for 88.4% of all patients and for 95.4% of patients observed during 2000 to 2005. We did not have individual data on HCV infection in the general population, but the estimated prevalence in Denmark is only 3 per 1000 (13). Highly active antiretroviral therapy was defined as the combination of antiretroviral treatment with at least 3 drugs, including at least 1 protease inhibitor, 1 nonnucleoside reverse transcriptase inhibitor, or abacavir; or the 2-drug combination of efavirenz-

and ritonavir-boosted lopinavir. Treatment interruption was defined as a period of at least 2 weeks after initiation of HAART during which the patient did not take antiretroviral drugs. Structured treatment interruptions have generally not been recommended in Denmark. Causes of death extracted from patient files were available for patients in DHCS and were divided into HIV-related causes (AIDS-defining illnesses and bacterial infections, corresponding to International Classification of Disease, Tenth Revision [ICD-10], codes A02, A07.2-07.3, A15-19, A31, A81.2, B00, B20-25, B37-39, B45, B58, C46, C53, C83.4, C83.9, F02.4, and J13-17), non-HIV-related other causes, and unknown causes.

Statistical Analysis

We computed Kaplan–Meier life tables using age as the time scale. Persons with HIV infection were observed from the date of HIV diagnosis or from the first visit to an HIV clinic, if the visit occurred at a later date; persons from the general population were observed starting at the same time as their matched HIV-infected patients. All persons were censored at emigration or on 1 May 2005. Death from any cause was the outcome event.

We estimated median survival times and computed mortality rates from age 25 years separately for men and women and for the subgroup of HCV-negative persons. We chose 25 years because this was the youngest age group with a sufficient number of patients ($n = 170$) being observed. We performed analyses for 3 clinically relevant periods: 1995 to 1996 (pre-HAART), 1997 to 1999 (early HAART), and 2000 to 2005 (late HAART) and with respect to the length of HAART treatment: before HAART, first year, second and third years, fourth and fifth years, and sixth year onward.

We computed mortality rates in 5-year age intervals and estimated crude relative (mortality rate ratio [mortality rate for patients with HIV infection divided by the mortality rate for the general population]) and absolute (excess mortality rate [mortality rate for the general population subtracted from the mortality rate for patients with HIV infection]) effects in HIV-infected patients compared with persons from the general population. In accordance with the matched design, we used a stratified Cox regression model for the mortality rate ratio estimations. When comparing mortality rate ratios from the stratified model with crude mortality rate ratios, we found only small deviations (median, 4.3% [interquartile range, 1.2% to 7.0%]) and therefore used standard statistical methods for the excess mortality rates. We further examined mortality rate ratios and excess mortality rates for the late HAART period and for HCV-negative and HCV-positive persons during the late HAART period.

Data analysis was performed by using Stata statistical software, version 9.0 (Stata Corp., College Station, Texas).

Table 1. Characteristics of Study Participants*

Variable	Patients with HIV Infection	General Population without HIV Infection
Persons, <i>n</i>	3990	379 872
Men, %	77	77
Median age at study entry (interquartile range), <i>y</i>	37.2 (31.0–44.8)	36.9 (30.9–44.6)
Median observation time (interquartile range), <i>y</i>	5.8 (2.2–9.9)	8.4 (4.3–10.3)
Incident cases (diagnosed after 1 January 1995), <i>n</i> (%)	2045 (51)	–
Entered the cohort within 31 days after diagnosis	1556 (76)	–
Entered the cohort within 181 days after diagnosis	1943 (95)	–
Most likely method of infection, <i>n</i> (%)		
Male homosexual activity	1863 (47)	–
Heterosexual activity	1377 (35)	–
Intravenous drug use	480 (12)	–
Other	270 (7)	–
Race, <i>n</i> (%)		
Caucasian	3287 (82)	NA
Black	446 (11)	NA
Other	257 (6)	NA
Positive for hepatitis C infection	668 (17)	–

* HIV = human immunodeficiency virus; NA = not available.

Approvals and Permissions

The Danish Data Protection Agency approved the establishment of the cohort study. The study was not subject to approval by the ethics committee because data collection did not involve direct patient contact.

Role of the Funding Sources

The Danish HIV Cohort study receives funding from the Danish AIDS Foundation, Odense University Hospital, Preben and Anna Simonsen's Foundation, the Foundation of the Danish Association of Pharmacists, and the Clinical Institute at the University of Southern Denmark. The funding sources were not involved in the design, data collection, analysis, or writing of the study.

RESULTS

Study Sample

We included 3990 HIV-infected persons and 379 872 persons from the general population: The respective median observation time after age 25 years was 5.8 person-years (interquartile range, 2.2 to 9.9 person-years) and 8.4 person-years (interquartile range, 4.3 to 10.3 person-years), respectively (Table 1). One hundred twenty-one (3.0%) HIV-infected patients and 11 552 (3.0%) persons from the general population were lost to follow-up; of these, 107 (2.7%) patients with HIV infection and 10 234 (2.7%) persons from the general population emigrated. There were 2045 (51%) incident HIV cases diagnosed after 1 January 1995; 75% were observed within 31 days of diagnosis, and 95% came under observation within the first 181 days after diagnosis. After HAART was introduced in 1996, the prevalence of patients receiving this treatment gradually increased, surpassing 75% in 2002 to 2004. At any given time, fewer than 5% of HIV-infected patients were interrupting treatment. The number of patients under observation varied with age and was highest (range, 515 to 1004) for those who were 30 to 50 years of age (Table 2).

Survival from Age 25 Years

All participants were observed from age 25 years: HIV-infected persons had a median survival of 19.9 years (17.5 years for men and 24.2 years for women), whereas persons from the general population had a median survival of 51.1 years (50.8 years for men and 54.8 years for women) (Table 3). During the late HAART period (2000 to 2005), median survival of HIV-infected patients had increased to 32.5 years (32.1 years for men and 32.3 years for women) overall, and to 38.9 years (37.8 years for men and 40.1 years for women) after persons with known HCV infection were excluded (Figure).

Mortality Rates

The mortality rate was 43 per 1000 person-years (95% CI, 40 to 45) for HIV-infected persons and 4.7 per 1000 person-years (CI, 4.6 to 4.8) for the general population (Table 3). The highest mortality rate, 124 per 1000 person-years (CI, 112 to 137), was observed in the pre-HAART period (1995 to 1996). This rate decreased to 38 per 1000 person-years (CI, 33 to 43) in the early HAART period (1997 to 1999) and to 25 per 1000 person-years (CI, 23 to 28) in the late HAART period (2000 to 2005). In patients receiving HAART, the highest mortality rate of 48 per 1000 person-years (CI, 40 to 57) was observed during the first year of treatment but decreased to 27 per 1000 person-years (CI, 22 to 32) during the second and third years of HAART, to 26 per 1000 person-years (CI, 21 to 32) during the fourth and fifth years of HAART, and to 26 per 1000 person-years (CI, 21 to 31) from the sixth year onward. Mortality rates were even lower among patients treated during the late HAART period. Although mortality rates declined with calendar time, we found no change in mortality rates from the first to the tenth year after the diagnosis of HIV infection. In the late HAART period, the mortality rate was 26 per 1000 person-years (CI, 19 to 34) during the first 2 years after diagnosis, 17

Table 2. Age-Specific Mortality Rates*

Variable	Age			
	25–30 y	>30–35 y	>35–40 y	>40–45 y
Under observation at the beginning of each age period, n				
Patients with HIV infection	170	566	959	950
General population	17 045	60 322	107 786	112 343
PYR (in thousands), n				
Patients with HIV infection	1.77	3.97	4.92	4.13
General population	184	432	567	505
Events, n				
Patients with HIV infection	54	113	176	189
General population	128	385	761	1296
Mortality rate for patients with HIV infection, per 1000 PYR	30.5 (23.4 to 39.9)	28.5 (23.7 to 34.3)	35.8 (30.8 to 41.4)	45.7 (39.7 to 52.7)
Mortality rate for general population, per 1000 PYR	0.7 (0.6 to 0.8)	0.9 (0.8 to 1.0)	1.3 (1.3 to 1.4)	2.6 (2.4 to 2.7)
Mortality rate ratio (patients vs. general population)	44.53 (32.0 to 61.9)	32.04 (25.9 to 39.7)	27.4 (23.1 to 32.4)	18.04 (15.4 to 21.1)
Excess mortality rate (patients vs. general population, per 1000 PYR)	29.8 (21.7 to 38.0)	27.6 (22.3 to 32.9)	34.4 (29.1 to 39.7)	43.2 (36.6 to 49.7)
Patients observed during the years 2000–2005				
Patients with HIV infection, PYR (in thousands)	0.77	1.98	3.04	2.58
Mortality rate for patients with HIV infection, per 1000 PYR	6.5 (2.7 to 15.6)	11.6 (7.7 to 17.5)	17.4 (13.3 to 22.8)	24.0 (18.7 to 30.8)
Mortality rate for general population, per 1000 PYR	0.6 (0.5 to 0.8)	0.8 (0.7 to 0.9)	1.2 (1.1 to 1.3)	2.3 (2.1 to 2.4)
Mortality rate ratio (patients vs. general population)	8.88 (3.2 to 24.7)	15.14 (9.7 to 23.5)	14.36 (10.7 to 19.3)	10.55 (8.1 to 13.8)
Excess mortality rate (patients vs. general population), per 1000 PYR	5.8 (1.6 to 11.5)	10.9 (6.1 to 15.6)	16.2 (11.5 to 20.9)	21.8 (15.8 to 27.8)
HCV-negative patients observed during the years 2000–2005				
Patients with HIV infection, PYR (in thousands)	0.67	1.66	2.45	1.99
Mortality rate for patients with HIV infection, per 1000 PYR	1.5 (0.2 to 10.6)	8.5 (5.0 to 14.3)	13.5 (9.6 to 19.0)	14.1 (9.7 to 20.4)
Mortality rate for general population, per 1000 PYR	0.6 (0.5 to 0.8)	0.8 (0.7 to 0.9)	1.2 (1.1 to 1.3)	2.3 (2.1 to 2.5)
Mortality rate ratio (patients vs. general population)	2.6 (0.4 to 19.3)	10.7 (6.2 to 18.6)	11.5 (8.0 to 16.6)	6.3 (4.3 to 9.3)
Excess mortality rate (patients vs. general population), per 1000 PYR	0.9 (–2.1 to 3.8)	7.7 (3.2 to 12.1)	12.3 (7.7 to 16.9)	11.8 (6.5 to 17.0)
HCV-positive patients observed during the years 2000–2005				
Patients with HIV infection, PYR (in thousands)	0.10	0.32	0.59	0.59
Mortality rate for patients with HIV infection, per 1000 PYR	38.5 (14.5 to 102.7)	28.2 (14.7 to 54.2)	33.7 (21.7 to 52.2)	57.8 (41.3 to 81.0)
Mortality rate for general population, per 1000 PYR	0.8 (0.4 to 1.6)	0.7 (0.5 to 1.0)	1.3 (1.1 to 1.6)	2.1 (1.8 to 2.5)
Mortality rate ratio (patients vs. general population)	41.6 (10.8 to 160.9)	42.1 (19.2 to 92.6)	24.5 (14.8 to 40.6)	24.4 (16.6 to 35.8)
Excess mortality rate (patients vs. general population), per 1000 PYR	37.8 (0.0 to 75.5)	27.5 (9.1 to 46.0)	32.4 (17.6 to 47.2)	55.7 (36.3 to 75.2)

* Values in parentheses are 95% CIs. HCV = hepatitis C virus; HIV = human immunodeficiency virus; NA = not available; PYR = person-years at risk.

per 1000 person-years (CI, 12 to 24) during the third and fourth years, 18 per 1000 person-years (CI, 13 to 25) during the fifth and sixth years, 21 per 1000 person-years (CI, 15 to 29) during the seventh and eighth years, and 17 per 1000 person-years (CI, 11 to 25) during the ninth and tenth years after diagnosis. Persons with HIV and HCV coinfection had considerably higher mortality rates than those who were HCV-negative (mortality rate, 59 [CI, 52 to 67] vs. 39 [CI, 36 to 42]), and this finding was even more marked in the late HAART period (mortality rate, 57 [CI, 48 to 67] vs. 19 [CI, 17 to 22]).

Age-Specific Mortality Rates

Mortality rates increased with age for HIV-infected persons and for the general population (Table 2). Among HCV-negative persons with HIV infection who were younger than 50 years, mortality rates during the late HAART period did not exceed 15.0 per 1000 person-years (CI, 10.0 to 22.6).

The mortality rates for HIV-infected persons relative to those for the general population (mortality rate ratio) were highest in the younger age groups. The decrease in mortality rate ratio with age was driven by the natural age-dependent increase in mortality rates in the reference population. The mortality rate ratio decreased from 44.5 (CI, 32.0 to 61.9) for persons who were age 25 to 30 years to 3.4 (CI, 2.3 to 5.1) for those who were age 65 to 70 years. Among persons observed in the late HAART period, the mortality rate ratio varied from 15.1 (CI, 9.7 to 23.5) to 3.0 (CI, 2.0 to 4.6) for all HIV-infected patients. After HCV-positive persons were excluded, the mortality rate ratio during this period ranged from 11.5 (CI, 8.0 to 16.6) to 2.8 (CI, 2.0 to 4.0).

In contrast to the age-related decrease in mortality rate ratio, the excess mortality rate for HIV-infected patients compared with that for the general population was lowest in the younger age groups and increased with age. The

Table 2—Continued

Age				
>45–50 y	>50–55 y	>55–60 y	>60–65 y	>65–70 y
727 90 759	517 65 254	373 45 872	224 27 170	77 11 023
3.07 386	2.26 280	1.53 185	0.67 86	0.28 40
155 1795	111 2036	69 2031	49 1543	26 1169
50.5 (43.1 to 59.1)	49.2 (40.8 to 59.2)	45.2 (35.7 to 57.3)	73.4 (55.4 to 97.1)	93.1 (63.4 to 136.7)
4.7 (4.4 to 4.9)	7.3 (7.0 to 7.6)	11.0 (10.5 to 11.4)	18.0 (17.1 to 18.9)	29.1 (27.5 to 30.8)
10.81 (9.1 to 12.8)	7.24 (6.0 to 8.8)	4.05 (3.2 to 5.2)	4.23 (3.2 to 5.6)	3.43 (2.3 to 5.1)
45.9 (37.9 to 53.8)	41.9 (32.7 to 51.0)	34.3 (23.6 to 45.0)	55.4 (34.8 to 75.9)	64.0 (28.2 to 99.8)
1.93 32.2 (25.1 to 41.3)	1.40 33.5 (25.2 to 55.6)	1.14 34.3 (25.0 to 46.9)	0.51 49.3 (33.3 to 73.0)	0.18 81.3 (49.1 to 134.9)
4.5 (4.3 to 4.8)	7.1 (6.7 to 7.5)	10.6 (10.0 to 11.1)	17.0 (16.1 to 18.1)	28.5 (26.6 to 30.5)
6.81 (5.2 to 8.9)	5.14 (3.8 to 7.0)	3.16 (2.3 to 4.4)	3.04 (2.0 to 4.6)	3.11 (1.9 to 5.2)
27.6 (19.6 to 35.7)	26.4 (16.8 to 36.0)	23.7 (12.9 to 34.4)	32.3 (12.9 to 51.6)	52.8 (11.7 to 94.0)
1.53 15.0 (10.0 to 22.6)	1.22 27.8 (19.9 to 39.0)	1.10 30.1 (21.4 to 42.4)	0.49 47.0 (31.3 to 70.8)	0.18 82.3 (49.6 to 136.5)
4.6 (4.3 to 4.9)	7.0 (6.6 to 7.5)	10.6 (10.0 to 11.2)	17.0 (16.0 to 18.1)	28.5 (26.6 to 30.5)
3.0 (2.0 to 4.7)	4.3 (3.1 to 6.2)	2.8 (2.0 to 4.0)	3.0 (2.0 to 4.6)	3.1 (1.9 to 5.2)
10.4 (4.3 to 16.6)	20.8 (11.4 to 30.2)	19.5 (9.2 to 29.8)	30.0 (10.8 to 49.3)	53.8 (12.1 to 95.5)
0.40 98.5 (72.0 to 134.8)	0.18 71.3 (41.4 to 122.7)	0.04 141.3 (63.5 to 314.6)	0.02 109.9 (27.5 to 439.3)	0.00 NA
4.3 (3.8 to 4.9)	7.3 (6.4 to 8.3)	10.1 (8.0 to 12.8)	17.3 (13.0 to 23.0)	27.9 (20.4 to 38.0)
21.6 (15.2 to 30.8)	10.3 (5.7 to 18.8)	13.7 (5.3 to 35.5)	3.5 (0.5 to 26.0)	NA
94.2 (63.3 to 125.1)	64.0 (25.2 to 102.8)	131.2 (18.1 to 244.3)	92.6 (–59.8 to 244.9)	NA

excess mortality rate during the late HAART period was not higher than 12.3 per 1000 person-years (CI, 7.7 to 16.9) among HCV-negative persons who were younger than 50 years but increased gradually with age to 53.8 per 1000 person-years (CI, 12.1 to 95.5) among persons who were 65 to 70 years. These figures were 2- to 4-fold higher if all patients and observation years were included (Table 2).

Causes of Death

The mortality rate for HIV-related death decreased from 71 per 1000 person-years (CI, 63 to 81) in the early HAART period to 7.0 per 1000 person-years (CI, 5.8 to 8.6) in the late HAART period, and non-HIV-related deaths decreased from 23 per 1000 person-years (CI, 18 to 29) to 9.4 per 1000 person-years (CI, 7.9 to 11.2) (Table 4). Thus, the proportion of known causes of death that were related to HIV infection decreased from 76% in 1995

to 1996, to 57% in 1997 to 1999, and to 43% in 2000 to 2005.

DISCUSSION

In this population-based cohort study, we estimate a median remaining lifetime of more than 35 years for a 25-year-old, HIV-positive person without HCV infection who received care in the twenty-first century. We expect this estimate to be robust because the study included all patients, regardless of such prognostic factors as CD4-positive cell count, HIV RNA, disease stage, history of AIDS, treatment adherence, or time receiving HAART. The increase in survival over time was attributable mainly to a decrease in HIV-related deaths. Despite the encouraging survival expectations, the study still shows large, age-dependent excess mortality rates in the HIV-infected cohort compared with the general population. The excess mortal-

Table 3. Median Survival and Mortality Rates Starting at Age 25 Years*

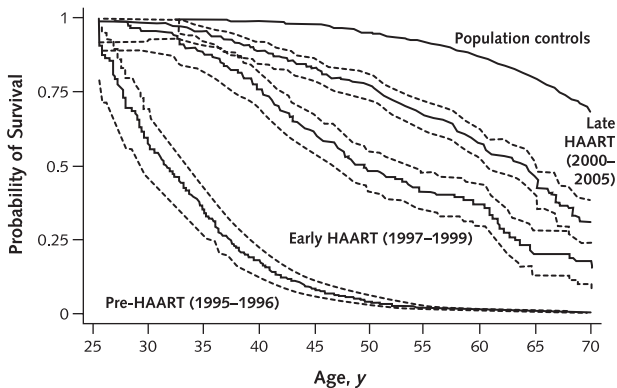
Variable	PYR	Events	Mortality Rate per 1000 PYR (95% CI)			Median Survival after Age 25 Years (95% CI), y		
			Total	Men	Women	Total	Men	Women
General population	2 689 287	12 565	4.7 (4.6–4.8)	5.5 (5.4–5.6)	1.8 (1.7–1.9)	51.1 (50.9–51.5)	50.8 (50.4–51.1)	54.8 (53.4–∞)
Patients with HIV infection	22 744	970	43 (40–45)	47 (44–50)	29 (25–34)	19.9 (18.5–21.3)	17.5 (15.4–19.3)	24.2 (21.6–26.6)
HAART period								
No HAART	8271	537	65 (60–71)	75 (68–82)	37 (30–46)			
1st year	2605	124	48 (40–57)	51 (42–62)	35 (23–54)			
2nd–3rd year	4534	121	27 (22–32)	28 (23–35)	21 (14–32)			
4th–5th year	3570	92	26 (21–32)	26 (21–33)	25 (16–39)			
6th year onward	3764	96	26 (21–31)	27 (22–34)	18 (11–31)			
Time since diagnosis								
1st–2nd years after diagnosis	3436	159	46 (40–54)	53 (44–62)	28 (19–42)			
3rd–4th years after diagnosis	3419	133	39 (33–46)	44 (36–53)	25 (17–38)			
5th–6th years after diagnosis	3136	116	37 (31–44)	40 (33–50)	28 (19–42)			
7th–8th years after diagnosis	2799	117	42 (35–50)	47 (39–58)	26 (16–41)			
9th–10th years after diagnosis	2614	129	49 (42–59)	56 (46–67)	30 (19–47)			
Hepatitis C status								
Positive	4149	246	59 (52–67)	68 (59–78)	44 (34–56)	17.6 (15.0–19.6)	15.3 (10.3–18.1)	21.6 (17.4–24.2)
Negative	18 595	724	39 (36–42)	43 (40–46)	24 (19–29)	21.0 (19.3–23.2)	18.5 (16.0–20.6)	27.4 (23.6–35.0)
Observation period								
1995–1996	3243	402	124 (112–137)	136 (122–151)	78 (60–103)	7.6 (4.8–9.6)	5.5 (3.4–8.5)	11.0 (6.3–12.9)
1997–1999	5857	222	38 (33–43)	41 (35–47)	28 (20–38)	22.5 (20.0–24.5)	22.1 (18.2–24.0)	24.6 (16.6–36.4)
2000–2005	13 644	346	25 (23–28)	27 (24–30)	20 (16–26)	32.5 (29.4–34.7)	32.1 (28.5–34.9)	32.3 (24.5–36.1)
Patients with HIV infection observed 2000–2005 only								
HAART period								
No HAART	2946	66	22 (18–29)	26 (20–34)	15 (9–26)			
1st year	1073	46	43 (32–57)	50 (37–69)	24 (11–50)			
2nd–3rd year	2464	57	23 (18–30)	23 (17–31)	23 (14–38)			
4th–5th year	3398	81	24 (19–30)	24 (18–30)	24 (15–38)			
6th year onward	3763	96	26 (21–31)	27 (22–34)	18 (11–31)			
Time since diagnosis								
1st–2nd years after diagnosis	1875	48	26 (19–34)	30 (22–40)	15 (8–31)			
3rd–4th years after diagnosis	1901	32	17 (12–24)	17 (11–26)	16 (9–32)			
5th–6th years after diagnosis	1786	32	18 (13–25)	16 (11–25)	22 (12–40)			
7th–8th years after diagnosis	1630	34	21 (15–29)	23 (16–33)	16 (7–33)			
9th–10th years after diagnosis	1439	24	17 (11–25)	18 (12–29)	12 (5–30)			
Hepatitis C status								
Positive	2245	127	57 (48–67)	59 (48–74)	52 (38–70)	19.6 (16.1–21.9)	19.3 (9.6–22.2)	21.1 (14.9–23.7)
Negative	11 399	219	19 (17–22)	22 (19–25)	10 (7–15)	38.9 (35.4–40.1)	37.8 (34.3–40.0)	40.1 (35.0–∞)

* HAART = highly active antiretroviral therapy; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PYR = person-years at risk.

ity rates increased with increasing age, whereas the relative mortality rates decreased.

Three previous studies have compared age- sex- and calendar-year-specific mortality rates of HIV-infected patients with those of the general population (2, 3, 14). In the Dutch ATHENA (AIDS Therapy Evaluation, the Netherlands Study Group) cohort (2), the overall mortality rate among HIV-infected patients was considerably lower (10.6 per 1000 person-years) than in our study; as in our study, the ATHENA cohort showed a pattern of decreasing

relative mortality rates with increasing age but no increase in the excess mortality rate with age. However, the study sample was restricted to antiretroviral-naive patients who had survived the first 24 weeks of a HAART regimen. In contrast, we included all patients, both those who were diagnosed with advanced disease and did not survive for 24 weeks and those who did not yet meet the criteria for HAART, which allowed us to estimate survival in the total HIV population. In the Swiss HIV Cohort Study, Jaggy and colleagues (14) studied excess mortality rates in pa-

Figure. Survival from age 25 years.

Cumulative survival curve for HIV-infected persons (without hepatitis C coinfection) and persons from the general population. Persons with HIV infection are divided into 3 calendar periods of observation. Dashed lines indicate 95% CIs. HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy.

tients “successfully treated with HAART” (excess mortality rate, 3.1 to 8.0 [HCV-negative] and 20.5 to 25.9 [HCV-positive] per 1000 person-years) vs. “unsuccessfully treated with HAART” (excess mortality rate, 117.4 [HCV-negative] and 112.7 [HCV-positive] per 1000 person-years). These authors did not report the distribution of ages in their study groups or the age-specific excess mortality rates. In another analysis based on the Swiss HIV Cohort Study, Keiser and colleagues (3) found a decrease in the mortality rate from 130 per 1000 person-years during 1990 to 1995 to 30 per 1000 person-years during 1997 to 2001, and a concomitant decrease in standardized mortality rate ratio from 79.3 to 15.3. There was a 21% withdrawal rate in that study, and no information was available regarding par-

ticipants’ age distributions. Because mortality rates among HIV-infected and noninfected persons are highly age-dependent, the age-specific mortality rates reported in our study allow transparency and easier comparison among studies and samples. Further, the 2 Swiss Cohort Study reports were based on data up to 2001 and did not incorporate the advances in treatment effectiveness obtained during the subsequent 4 years. Braithwaite and coworkers (15) used data from the Collaborations in HIV Outcomes Research/US (CHORUS) cohort (16) to develop a computer model that incorporated time-updated CD4-positive cell counts, viral load, adherence to treatment, and development of resistance; the estimated median survival from that model was 20.4 years for newly diagnosed patients. Compared with CHORUS, which is a clinic-based, multi-state cohort study requiring informed consent from the patients, DHCS is geographically based with almost complete inclusion of HIV-infected patients in our area. Therefore, we may interpret our findings as a result of the total health care effort in our area.

The mortality rates for HIV-infected patients may be put into clinical perspective by comparison with mortality rates among patients with type 1 diabetes mellitus, another serious chronic disease of young adults. Laing and coworkers (17) estimated age- and sex-specific mortality rates for patients with type 1 diabetes (per 1000 person-years). They reported the following mortality rates for women and men, respectively: for age 30 to 39 years, 3.2 and 4.2; for age 40 to 49 years, 8.5 and 11.6; for age 50 to 59 years, 19.1 and 26.2; and for age 60 to 69 years, 44.6 and 63.2. These rates are slightly lower than the rates we found among persons without HCV infection during the late HAART era.

The strengths of our study are its population-based setting, minimal participants lost to follow-up, high quality of the death registration (that is, we are certain that all

Table 4. Mortality Rates according to Cause of Death and Calendar Period*

Observation Period	Cause of Death	PYR, n	Events, n	Mortality Rate per 1000 PYR (95% CI)	All-Cause Mortality Rate, %	Mortality Rate by Known Causes, %
1995–1996						
	All causes	3243	402	124 (112–137)	100	
	HIV-related	3243	231	71.2 (62.6–81.0)	57	76
	Non-HIV-related	3243	75	23.1 (18.4–29.0)	19	24
	Unknown	3243	96	29.6 (24.2–36.2)	24	
1997–1999						
	All causes	5857	222	37.9 (33.2–43.2)	100	
	HIV-related	5857	104	17.8 (14.7–21.5)	47	57
	Non-HIV-related	5857	80	13.7 (11.0–17.0)	36	43
	Unknown	5857	38	6.5 (4.7–8.9)	17	
2000–2005						
	All causes	13 644	346	25.4 (22.8–28.2)	100	
	HIV-related	13 644	96	7.0 (5.8–8.6)	28	43
	Non-HIV-related	13 644	128	9.4 (7.9–11.2)	37	57
	Unknown	13 644	122	8.9 (7.5–10.7)	35	

* HIV = human immunodeficiency virus; PYR = person-years at risk.

dates were correct for all registered deaths), clearly defined date of inclusion of all prevalent and incident cases of HIV infection in Denmark (1 January 1995), and large proportion of incident cases observed shortly after patients were diagnosed with HIV infection, which allowed us to follow up on most patients from before initiation of HAART.

Despite the advantages of good-quality data, our study has limitations. First, survival predictions were based on the assumption that the observed mortality rates also would apply in subsequent years, whereas actual observation time of any individual patient was at most 10 years. However, we found no increase in mortality rates through the first 10 years of infection or increase in mortality rates with increasing time receiving HAART, and we found a decrease in mortality rates with increasing calendar period. These findings agree with a previous study from DHCS, in which we observed a decreasing incidence of triple-class drug failure with successive calendar periods (18). Thus, we did not see any signs of waning effectiveness of HAART, which is currently debated and considered to be a potential health threat because of multiclass drug failure, accumulation of drug resistance, and long-term drug toxicities (19, 20). Although our predictions reach far beyond the current experience with HIV and HAART, we saw no signs that a 50-year-old patient who was infected several years previously had a higher mortality rate than a recently infected 50-year-old patient. Second, some eligible HIV-infected persons may not have been included in the study. Because dispensing antiretroviral drugs in Denmark is restricted to HIV clinics and is free, many of the missed patients are probably those who do not fulfill the criteria for HAART and therefore have low mortality rates. This would cause overestimation of mortality rates in the HIV-infected cohort. In contrast, many patients may not seek care despite being eligible for antiretroviral treatment and may belong to a group with such comorbid conditions as mental health disorders or addiction problems. This group would have a higher risk for death, because of HIV infection and comorbid conditions, thus leading to an underestimation of the mortality rates in the HIV-infected cohort. Third, the HIV-infected population is thought to differ from the general population regarding socioeconomic and behavioral factors (8, 21) and having acquired HIV infection probably indicates a tendency toward risk behaviors. Studies have shown a higher frequency of smoking and alcohol consumption among HIV-infected patients (22, 23). Matching the cohort of persons from the general population according to sex, age, and place of residence may partly correct for these group differences, but any residual confounding by lifestyle or comorbid conditions would cause an overestimation of the observed excess mortality rates because of HIV infection. Fourth, the results are influenced by the composition of the study sample. In our cohort, and in most other HIV-infected populations, the mortality rates differ in subgroups (defined by HCV coinfection status, ethnicity, risk behaviors, and sex), and may

be influenced by the person's position on different time scales (age, time receiving HAART, and calendar time). To explore and clarify the effect of these covariates, we presented mortality rates in selected time strata. The subgroup with the best prognosis (persons without HCV coinfection) comprised 84% of all persons observed in the late HAART era and was therefore chosen as a clinically useful reference group.

The survival projections in our study depend on continuous treatment success beyond the 10 years of current experience with HAART. Further, with the easy access to HAART and HIV care in Denmark, our findings may represent a best-case scenario. Not all subgroups of patients have the same prognosis, and treatment must be individualized according to actual risk estimates. Our study suggests that most young persons with HIV infection can expect to survive for more than 35 years, but an ongoing effort is still needed to further reduce mortality rates in these persons.

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Acknowledgments: The authors thank the staff of their clinical departments for their continuous support and enthusiasm.

Grant Support: The Danish HIV Cohort study receives funding from the Danish AIDS Foundation, Odense University Hospital, Preben and Anna Simonsen's Foundation, the Foundation of the Danish Association of Pharmacists, and the Clinical Institute at the University of Southern Denmark.

Potential Financial Conflicts of Interest: *Consultancies:* J. Gerstoft (Roche, Glaxo, Abbott, Boehringer Ingelheim, Merck Sharp & Dohme, Swedish-Orphan Drugs); *Honoraria:* J. Gerstoft (Roche, Glaxo, Abbott, Boehringer Ingelheim, MSD, Swedish-Orphan Drugs); *Grants received:* N. Obel (Roche, Bristol-Meyers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Abbott, Boehringer Ingelheim, Janssen-Cilag, Swedish-Orphan Drugs).

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References

1. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, D'Arminio MA, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*. 2003;362:22-29. [PMID: 12853195]
2. van Sighem A, Danner S, Ghani AC, Gras L, Anderson RM, De Wolf F, et al. Mortality in patients with successful initial response to highly active antiretroviral therapy is still higher than in non-HIV-infected individuals. *J Acquir Immune Defic Syndr*. 2005;40:212-18. [PMID: 16186740]
3. Keiser O, Taffe P, Zwahlen M, Battegay M, Bernasconi E, Weber R, et al. All cause mortality in the Swiss HIV Cohort Study from 1990 to 2001 in com-

- parison with the Swiss population. *AIDS*. 2004;18:1835-43. [PMID: 15316345]
4. Jensen-Fangel S, Pedersen L, Pedersen C, Larsen CS, Tauris P, Møller A, et al. Low mortality in HIV-infected patients starting highly active antiretroviral therapy: a comparison with the general population. *AIDS*. 2004;18:89-97. [PMID: 15090834]
 5. Lohse N, Ladefoged K, Pedersen L, Jensen-Fangel S, Sørensen HT, Obel N. Low effectiveness of highly active antiretroviral therapy and high mortality in the Greenland HIV-infected population. *Scand J Infect Dis*. 2004;36:738-42. [PMID: 15513400]
 6. Press N, Tyndall MW, Wood E, Hogg RS, Montaner JS. Virologic and immunologic response, clinical progression, and highly active antiretroviral therapy adherence. *J Acquir Immune Defic Syndr*. 2002;31 Suppl 3:S112-7. [PMID: 12562032]
 7. Lundgren JD, Mocroft A, Gatell JM, Ledergerber B, D'Arminio MA, Hermans P, et al. A clinically prognostic scoring system for patients receiving highly active antiretroviral therapy: results from the EuroSIDA study. *J Infect Dis*. 2002;185:178-87. [PMID: 11807691]
 8. Lohse N, Hansen AB, Jensen-Fangel S, Kronborg G, Kvinesdal B, Pedersen C, et al. Demographics of HIV-1 infection in Denmark: results from the Danish HIV Cohort Study. *Scand J Infect Dis*. 2005;37:338-43. [PMID: 16051569]
 9. The Civil Registration System in Denmark. Accessed at www.cpr.dk/index/dokumenter.asp?o=7&cn=0&d=141&cs=5 on 3 September 2006.
 10. Frank L. Epidemiology. When an entire country is a cohort. *Science*. 2000;287:2398-9. [PMID: 10766613]
 11. National Center for Health Statistics. United States Life Tables, 2002. Accessed at www.cdc.gov/nchs/products/pubs/pubd/lftbls/life/1966.htm on 3 September 2006.
 12. Jensen-Fangel S, Pedersen C, Larsen CS, Tauris P, Møller A, Obel N. Changing demographics in an HIV-infected population: results from an observational cohort study in Western Denmark. *Scand J Infect Dis*. 2001;33:765-70. [PMID: 11728045]
 13. Christensen PB. [Epidemiology of hepatitis C]. *Ugeskr Laeger*. 1998;160:3529-32. [PMID: 9641037]
 14. Jaggy C, von Overbeck J, Ledergerber B, Schwarz C, Egger M, Rickenbach M, et al. Mortality in the Swiss HIV Cohort Study (SHCS) and the Swiss general population. *Lancet*. 2003;362:877-8. [PMID: 13678976]
 15. Braithwaite RS, Justice AC, Chang CC, Fusco JS, Raffanti SR, Wong JB, et al. Estimating the proportion of patients infected with HIV who will die of comorbid diseases. *Am J Med*. 2005;118:890-8. [PMID: 16084183]
 16. The Collaborations in HIV Outcomes Research/US (CHORUS) Cohort. Accessed at www.hivforum.org/uploads/cohorts/CHORUS%203May2005.pdf on 3 September 2006.
 17. Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burden AC, Waugh NR, et al. The British Diabetic Association Cohort Study, I: all-cause mortality in patients with insulin-treated diabetes mellitus. *Diabet Med*. 1999;16:459-65. [PMID: 10391392]
 18. Lohse N, Obel N, Kronborg G, Laursen A, Pedersen C, Larsen CS, et al. Declining risk of triple-class antiretroviral drug failure in Danish HIV-infected individuals. *AIDS*. 2005;19:815-22. [PMID: 15867496]
 19. Phillips AN, Dunn D, Sabin C, Pozniak A, Matthias R, Geretti AM et al. Long term probability of detection of HIV-1 drug resistance after starting antiretroviral therapy in routine clinical practice. *AIDS*. 2005;19:487-94. [PMID: 15764854]
 20. Zwahlen M, Lundgren JD. Commentary: Death in the era of potent antiretroviral therapy: shifting causes, new challenges. *Int J Epidemiol*. 2005;34:130-1. [PMID: 15649955]
 21. Saves M, Chene G, Ducimetiere P, Lepout C, Le Moal G, Amouyel P, et al. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. *Clin Infect Dis*. 2003;37:292-8. [PMID: 12856222]
 22. Galvan FH, Bing EG, Fleishman JA, London AS, Caetano R, Burnam MA, et al. The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study. *J Stud Alcohol*. 2002;63:179-86. [PMID: 12033694]
 23. Mamary EM, Bahrs D, Martinez S. Cigarette smoking and the desire to quit among individuals living with HIV. *AIDS Patient Care STDS*. 2002;16:39-42. [PMID: 11839217]

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