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Median survival and age-specific mortality of Danish HIV-infected individuals: a comparison with the general population

Contact information: Nicolai Lohse, MD Department of Infectious Diseases Odense University Hospital Sdr. Boulevard 29 DK-5000 Odense C Denmark Phone: +45-65411621 Fax: +45-66124305 E-mail: nicolai.lohse@ouh.fvns-amt.dk

Nicolai Lohse¹, Ann-Brit Eg Hansen¹, Gitte Pedersen², Gitte Kronborg³, Jan Gerstoff⁴, Henrik Toft Sørensen⁵, Michael Væth⁶, Niels Obel¹

¹Department of Infectious Diseases, Odense University Hospital, Odense, Denmark and University of Southern Denmark, Odense, Denmark. ²Department of Infectious Diseases, Århus University Hospital, Aalborg, Denmark. ³Department of Infectious Diseases, Hvidovre University Hospital, Hvidovre, Denmark. ⁴Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark. ⁵Department of Clinical Epidemiology, Århus University Hospital, Århus, Denmark, and Department of Epidemiology, Boston University, Boston, Massachusetts, USA. ⁶Department of Biostatistics, Århus University, Århus, Denmark

Introduction

Knowing the expected survival of HIV-infected patients is of major public health interest. Studies comparing the mortality of HIV-infected individuals with age- and gender-specific mortality in the general population have reported a three- to ten-fold increased mortality in successfully treated patients. The relative mortality, however, is highly dependent on the age distribution in the study population, and does not in itself answer questions about survival. We therefore aimed to estimate the median survival and age-specific mortality for an entire HIV-infected population, as compared with a population control cohort.

Methods

The Danish HIV Cohort Study (DHCS) is a prospective, nationwide, populationbased cohort study of all HIV-infected individuals treated in Danish HIV clinics since 1 January 1995. HIV treatment in Denmark is restricted to eight specialised centres, and the Danish health care system provides free taxsupported medical care, including antiretroviral treatment for HIV. Adult (older than 16 years) DHCS participants with residency in Denmark at the first contact to an HIV clinic were included in this study.

The Danish Civil Registration System (CRS) is a national registry of all Danish residents, containing information on date of birth, gender, residency, migration, and death. For each HIV patient, we drew from CRS records a random sample of population controls, matched on gender and date of birth, who were alive and living in the sample municipality as the patient on the date of diagnosis. We aimed to sample 99 controls for each HIV-infected individual.

Linking data from the population-based DHCS and the CRS allowed us to use product-limit methods, analogous to the period life tables used by national authorities when estimating median survival.

We computed Kaplan-Meier life tables using age as the time scale. HIVinfected individuals were observed from the date of diagnosis with HIV or from the first visit to an HIV clinic if this occurred at a later date; members of the population cohort were observed starting at the sametime as their matched HIV patients. All individuals 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 (MR) from age 25 years, separately for men and women, and for the subgroup of HCVnegative individuals. We chose 25 years as the youngest age with a sufficient number of patients (170) under observation. We performed analyses for three clinically relevant periods: 1995-96 (pre-HAART), 1997-99 (early-HAART), and 2000-05 (late-HAART), and with respect to the length of HAART treatment: before HAART, 1st year, 2nd-3rd years, 4th-5th years, and 6th year or more. We computed MR in five-year age intervals and estimated crude relative (mortality rate ratios, MRR) and absolute (excess MR, EMR) effects comparing HIV patients with controls.

HIV-infected individuals were followed from before initiation of HAART, and included patients with such predictors of lower survival as poor response to therapy, AIDS diagnosis, low CD4 count, high viral load, and poor adherence.

Results

Study population We included 3,990 HIV-infected individuals and 379,872 general-population controls, with respective median observation time after age 25 of 5.8 (interquartile range [IQR]: 2.2-10.0) and 8.4 (IQR: 4.3-10.3) person-years. One hundred and twenty-one (3.0%) HIV patients and 11,552 (3.0%) controls were lost to follow-up.

Survival from age 25 years

Observed from age 25 years, HIV-infected individuals had a median survival of 19.9 years (males: 17.5, females: 24.2), while the general population had a median survival of 51.1 years (males: 50.8, females: 54.8) (Table 1). During the late-HAART period (2000-05), median survival of HIV patients had increased to 32.5 years (males: 32.1, females: 32.3) overall, and to 38.9 years (males: 37.8, females: 40.1) after excluding known HCV-positive individuals (Figure 1).

Mortality rates

The mortality rate was 43 per 1000 person-years (PYR) for the HIV-infected individuals, and 4.7 per 1000 PYR for the general population (Table 1). The highest MR – 124 per 1000 PYR –was observed in the pre-HAART period (1995-96), falling to 38 in the early-HAART period (1997-99), and to 25 in the late-HAART period (2000-05). In patients under HAART treatment, the highest MR of 48 per 1000 PYR was observed during the first year of treatment, but it fell to 27 during the 2nd-3rd year of HAART, to 26 during the 4th-5th year of HAART, and to 26 from the 6th year of HAART onwards. Mortality was even lower among patients treated with HAART during the late-HAART period (Table 1).



Figure 1 Survival from age 25 years. Cumulative survival curve for HIV-infected individuals and general-population controls HIV-infected individuals are divided into three calendar periods of observation.

Median survival and mortality rates starting at age 25 years	Tab	le 1							
			MR per 1000 PYR (95% CI)			Median survival (years) after age 25 years			
	PYR	events	total	mates	females	total	males	female	
Seneral									
population									
All	2689287	12565	4.7(4.6-4.8)	5.5(5.4-5.6)	1.8(1.7-1.9)	51.1	50.8	54.8	
ilV salarhi									
All	22744	920	43(45,45)	47144-501	29/25-343	19.9	12.6	24.2	
HCV-negative	18595	724	39/36-425	43(40,46)	24/19.295	21.0	18.5	27.4	
HAART period			20122-001	49(40-40)	24(1525)				
1st year of HAART	2605	124	48(40-57)	51(42-52)	35(23-54)				
2nd-3rd year of HAART	4534	121	27(22-32)	28(23-35)	21(14-32)				
4th-5th year of HAART	3570	90	26(21-32)	26/21-331	25(16,39)				
6th year of HAART prevants	3764	96	26(21-31)	27(22-34)	10(11-31)				
			20121-011	a. (e.e)					
No HAART	8271	537	65(60-71)	75(68-82)	37(30-45)				
Observation period									
			124(112-	136(122-					
Observed 95-95	3242	402	137)	151)	78(60-103)	7.6	5.5	11.0	
Observed 97-99	5857	222	38(33-43)	41(35-47)	28(20-38)	22.5	22.1	24.6	
Observed 00-05	13644	346	25(23-28)	27(24-30)	20(16-25)	32.5	32.1	32.2	
Subgroups observed 60-05:									
1st year of HAART	1073	46	43(32-57)	50(37-69)	24(11-50)				
2nd-3rd year of HAART	2454	57	23(18-30)	23(17-31)	23(14-38)				
4th-5th year of HAART	3398	81	24(19-30)	24(18-30)	24(15-38)				
6th year of HAART onwards	3763	96	26(21-31)	27(22-34)	18(11-31)				
NO HAART	2946	66	22(18-29)	25(20-34)	15(9-26)				
HCV-negative individuals observed during the years 2000-2	2005								
	11399	219	19(17-22)	22(19-25)	10(7-15)	38.9	37.8	40.1	
HIV: human immunodeficiency virus									
PYR: person-years at risk									
MR: mortality rate									
HCV: hepatitis C virus									
HAART: highly active antiretroviral therapy									

servation at the beginning of period HIV-patients General population HIV-patients General population	25-30 170 17045	30-35 566 60322	35-40	40-45	45-50	50-55	55-60	60-65	65-7
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HIV-patients General population thousands) HIV-patients General population	170 17045	566 60322	959	10.00					
General population thousands) HIV-patients General population	17045	60322		950	727	517	373	224	- 77
HIV-patients General population			107786	112343	90759	65254	45872	27170	110
HIV-patients General population									
General population	1.77	3.97	4.92	4.13	3.07	2.26	1.53	0.67	0.2
	184	432	567	505	386	280	185	86	- 4
HIV-patients	54	113	176	189	155	111	69	49	- 2
General population	128	385	761	1296	1795	2036	2031	1543	11
000 PYR)									
HIV-patients	30.5	28.5	35.8	45.7	50.5	49.2	45.2	73.4	- 93
General population	0.7	0.9	1.3	2.6	4.7	7.2	11.0	18.0	- 29
	44.2	32.0	26.7	17.8	10.9	6.8	4.1	4.1	3.
1000 PYR)	29.8	27.6	34.5	43.1	45.9	41.9	34.2	55.4	64
ears 2000-2005									
000 PY/R)									
HIV-patients	6.5	11.6	17.4	24.0	32.2	33.5	34.3	49.3	81
General population	0:6	0.8	1.2	2.3	4.5	7.1	10.6	17.0	28
	10.1	14.9	14.5	10.6	7.1	4.7	3.2	2.9	2
1000 PYR)	5.8	10.8	16.2	21.7	27.7	26.4	23.8	32.3	57
nts observed during the years									
000 PY/R)									
HIV-patients	1.5	8.5	13.5	14.1	15.0	27.8	30.1	47.0	82
General population	0.6	0.8	1.2	2.3	4.6	7.0	10.6	17.0	20
	2.5	10.6	11.5	6.1	3.3	4.0	2.8	2.8	2
1000 PYR)	0.9	77	12.3	11.8	10.4	20.8	19.5	30.0	53
	Hork-patients Generral population Hork-patients Generral population Hork patients Generral population Hold patients Generral population Hork patients Generral population	000 PYR) 30.5 Overlag population 0.7 1000 PYR) 22.8 1000 PYR) 23.8 1000 PYR) 5.8 000 PYR) 6.5 000 PYR) 6.8 000 PYR) 6.8 000 PYR) 5.8 ensis observed during the years 1.5 Oceneral population 6.5 1000 PYR) 5.8 1000 PYR) 5.8 1000 PYR) 6.5 000 PYR) 6.5 000 PYR) 6.5 000 PYR) 0.5 1000 PYR) 0.5 000 PYR 0.5 000 PYR 0.5 000 PYR 0.5	000 PYR) 30.5 28.5 General population 42.7 9.9 1000 PYR) 22.8 27.6 1000 PYR) 23.8 27.6 1000 PYR) 25.8 27.6 1000 PYR) 6.5 11.6 000 PYR) 6.5 14.6 000 PYR) 5.8 10.9 1000 PYR) 5.8 10.9 1000 PYR) 5.8 5.5 Central population 6.5 11.6 1000 PYR) 1.5 8.5 General population 1.5 8.5 1000 PYR) 1.5 9.7 1000 PYR) 9.7 7.7 000 PYR) 9.7 7.7 000 PYR) 9.7 7.7 000 PYR) 9.9 7.7 000 PYR) 9.9 7.7 000 PYR) 9.9 7.7	000 PPR) 30.5 28.5 3.5.8 General population 0.7 9.9 1.3 44.2 2.0 25.7 3.42 1000 PPR) 2.9 2.7.6 3.42 000 PPR) 2.9 2.7.6 3.42 000 PPR) 6.5 11.6 17.4 000 PPR) 0.5 0.8 13 000 PPR) 0.6 1.3 1.4 000 PPR) 1.0 1.4.9 1.6.3 000 PPR) 1.5 8.5 13.6 000 PPR) 1.5 8.5 13.5 000 PPR) 0.5 0.6 1.3 1000 PPR) 1.5 8.5 13.5 000 PPR) 0.5 0.7 7.7 1000 PPR) 0.9 7.7 7.3 1000 PPR) 0.9 9.7 7.3 000 PPR) 0.9 9.7 7.3	D00 PPR) PVP, patients Over employed and/or PVPR) 28.5 29.8 29.8 29.8 29.8 29.8 29.8 29.8 29.8	000 PPR) 0.5 28.5 35.8 45.7 50.3 0eners population 0.7 9.9 1.3 2.6 4.7 1000 PPR) 2.7 2.0 2.7 1.7 1.03 1000 PPR) 2.7 2.7 3.4 4.3 4.3 000 PPR) 2.7 2.6 1.6 1.7 4.2 000 PPR) 6.5 1.6 7.4 2.0 2.7 000 persy 6.5 1.6 7.4 2.0 2.7 000 persy 6.5 1.6 7.4 2.0 2.7 000 persy 6.5 1.6 1.6 2.1 2.7 000 persy 5.8 1.0 8 1.6 7.1 000 persy 5.8 1.6 1.5 2.1 2.7 100 persy 5.8 5.5 1.5 1.4 1.5 0.6 0.6 1.3 2.3 4.4 1.5 0.6 0.6 0.6	D00 PPR) Development (event population 20.5 2.2.5 28.5 2.5 35.8 2.5 45.7 2.5 55.8 2.5 45.7 2.5 55.8 2.5 45.7 2.5 26.7 2.5 27.6 2.5 28.7 2.5 28.7 2.5 28.7 2.5 28.7 2.5 28.7 2.5 28.7 2.5 28.7 2.5 28.5 45.7 49.2 2.5 49.2 2.5 D00 PVR) HVX pattering D00 PVR) HVX pattering HVX	D00 PPR) HN - putteris Overhar population D 5 0 7 42 25 0 8 55 0 8 45 2 8 7 2 8 55 0 8 45 2 8 7 2 8 2 0 8 45 2 8	D00 PPR) Determine population 30.5 26.5 35.8 45.7 55.8 49.2 45.2 73.4 0 energi population 42.2 25.0 26.7 17.8 10.9 47.2 11.9 18.9 1000 PPR() 22.8 27.6 34.5 45.1 45.9 41.9 34.2 55.4 000 PPR() 22.8 27.6 34.5 45.1 45.9 41.9 34.2 55.4 000 PPR() 6.5 11.6 17.4 24.0 23.2 25.7 34.5 45.5 000 PPR() 16.1 14.9 14.5 10.6 7.1 4.7 32.2 29 000 PPR() 16.8 12.6 21.7 27.7 26.4 23.8 29 000 PPR() 15.8 15.5 14.1 15.0 27.8 30.1 47.0 000 PPR() 5 0.9 12.2 21.4 27.8 30.1 47.0 000 PPR() 15 8.5 13.

Conclusion and Interpretation

In this population-based cohort study we estimate a median remaining lifetime of 38.9 years for a 25-year old HIV-positive, HCV-negative individual who was under care in the 21st century.

- We expect this estimate to be robust, because the study included all patients, regardless of prognostic factors, such as CD4+ cell count, HIV RNA, CDC stage, history of AIDS diagnosis, treatment adherence, or time on HAART.
- The excess mortality increased with increasing age, while the relative mortality decreased.
- The survival projections in our study depend upon continuous treatment success beyond the 10 years of current experience with HAART.
- · Not all subgroups of patients carry the same prognosis, and treatment must be individualised according to actual risk estimates.
- Despite the encouraging survival expectations, an ongoing effort is still needed to further reduce mortality of HIV-infected individuals.

Table 2

Age-specific mortality rates

Age period		25-30	30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70
All patients										
Under obser each age pe	rvation at the beginning of priod									
	HIV-patients	170	566	959	950	727	517	373	224	77
	General population	17045	60322	107786	112343	90759	65254	45872	27170	11023
PYR (in tho	usands)									
	HIV-patients	1.77	3.97	4.92	4.13	3.07	2.26	1.53	0.67	0.28
	General population	184	432	567	505	386	280	185	86	40
Events										
	HIV-patients	54	113	176	189	155	111	69	49	26
	General population	128	385	761	1296	1795	2036	2031	1543	1169
MR (pr 1000) PYR)									
	HIV-patients	30.5	28.5	35.8	45.7	50.5	49.2	45.2	73.4	93.1
	General population	0.7	0.9	1.3	2.6	4.7	7.2	11.0	18.0	29.1
MRR		44.2	32.0	26.7	17.8	10.9	6.8	4.1	4.1	3.2
EMR (pr 100	EMR (pr 1000 PYR)		27.6	34.5	43.1	45.9	41.9	34.2	55.4	64.0
Patients observed year	rs 2000-2005									
MR (pr 1000) PYR)									
	HIV-patients	6.5	11.6	17.4	24.0	32.2	33.5	34.3	49.3	81.3
	General population	0.6	0.8	1.2	2.3	4.5	7.1	10.6	17.0	28.5
MRR		10.1	14.9	14.5	10.6	7.1	4.7	3.2	2.9	2.9
EMR (pr 100	00 PYR)	5.8	10.8	16.2	21.7	27.7	26.4	23.8	32.3	52.9
HCV-negative patients	observed during the years									
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MR (pr 1000) PYR)									
	HIV-patients	1.5	8.5	13.5	14.1	15.0	27.8	30.1	47.0	82.3
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MRR		2.5	10.6	11.5	6.1	3.3	4.0	2.8	2.8	2.9
EMR (pr 100	00 PYR)	0.9	7.7	12.3	11.8	10.4	20.8	19.5	30.0	53.9

HIV: human immunodeficiency virus PYR: person-years at risk MR: mortality rate MRR: mortality rate ratio EMR: excess mortality rate HCV: hepatitis C virus

Table 1

Median survival and mortality rates starting at age 25 years

			MR per 1000 PYR (95% CI)			Median survival (years) after age 25 years		
	PYR	events	total	males	females	total	males	females
General								
population								
All	2689287	12565	4.7(4.6-4.8)	5.5(5.4-5.6)	1.8(1.7-1.9)	51.1	50.8	54.8
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No HAART	2946	66	22(18-29)	26(20-34)	15(9-26)			
HCV-negative individuals observed during the years 20	000-2005							
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HIV: human immunodeficiency virus

PYR: person-years at risk MR: mortality rate HCV: hepatitis C virus HAART: highly active antiretroviral therapy

Figure legends

Figure 1

Survival from age 25 years. Cumulative survival curve for HIV-infected individuals and general-population controls. HIV-infected individuals are divided into three calendar periods of observation.