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ORIGINAL RESEARCH

The burden of non-communicable diseases and mortality in people living with HIV (PLHIV) in the pre-, early- and late-HAART era

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Objectives

To estimate the burden of non-communicable diseases (NCDs) and mortality among PLHIV in the pre-, early- and late-HAART (highly active antiretroviral therapy) era.

Methods

We conducted a cohort study using population-based Danish medical registries including all adult HIV-infected residents of the Central Denmark Region during 1985–2017. For each HIV patient, we selected 10 comparisons from the background population matched by age, sex and municipality of residence. Based on hospital-related diagnoses we estimated the prevalence and incidence of specific NCD at diagnosis and at 5 and 10 years.

Results

We identified 1043 PLHIV and 10 430 matched comparisons. PLHIV had lower socioeconomic status and more were born outside western Europe. At HIV diagnosis, 21.9% of PHLIV *vs.* 18.2% of non-HIV individuals had at least one NCD, increasing to 42.2% *vs.* 25.9% after 10 years. PLHIV had higher prevalence and cumulative incidence of alcohol abuse, chronic obstructive pulmonary disease (COPD), ischaemic heart disease, mental disorders, renal and liver disease, but no increased risk of diabetes mellitus. Only PLHIV in the age groups 41–50 and > 51 years had an increased incidence of osteoporosis. From the pre- to the late-HAART era, 10-year mortality among PLHIV decreased from 45.5% to 9.4% but continued at more than twice that of uninfected comparisons. However, in the late-HAART era, the mortality of PLHIV who were alive 2 years after HIV diagnosis was approaching that of comparisons.

Conclusions

Even in the late-HAART era, PLHIV have an excess mortality, which may be attributable to several NCDs being more prevalent among PLHIV. The prevalence rates of ischaemic heart disease, diabetes, osteoporosis and renal disease tend to increase over calendar time. Therefore, improvement of survival and quality of life of PLHIV neets strategies to reduce the risk of developing NCDs, including avoiding toxic antiretroviral therapy and lifestyle changes.

Keywords: chronic obstructive pulmonary disease, diabetes mellitus, HIV, ischaemic heart disease, liver disease, mental disorders, mortality, non-communicable diseases, osteoporosis, renal disease

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Introduction

Antiretroviral therapy (ART) has resulted in HIV infection becoming a chronic medical condition. The life expectancy of people living with HIV (PLHIV) has gradually improved, approaching that of the general population [1,2]. Consequently, PLHIV are surviving to older age and requiring lifelong care and treatment. The proportion of PLHIV > 50 years old is predicted to increase to 73% in 2030 [3].

Despite a dramatic decrease in HIV/AIDS-related mortality, even well-treated PLHIV have a decreased life expectancy compared with individuals without HIV [4,5]. HIV/AIDS-related deaths remain high in the first year after HIV diagnosis, primarily among late presenters. However, after the first year of ART, the excess mortality is primarily caused by non-communicable diseases (NCDs) [6,7].

Across all age groups, PLHIV have a disproportionate risk of NCDs, mental disorders, and alcohol- and substance-use disorders [1,8–10]. This may be caused by a higher prevalence of traditional risk factors for chronic diseases such as tobacco and alcohol use, risk behaviour related to HIV transmission, intrinsic to HIV or ART-related toxicities [11]. Unhealthy lifestyle has been shown to be more frequent among PLHIV than among the general population [12–14]. Chronic inflammation has been associated with premature ageing and may predispose to NCDs [15]. The prevalence of NCDs in PLHIV may correspond to that observed in HIV-uninfected people who are 10 years older [16]. Also, antiretroviral drugs have been implicated in the development of cardiovascular disease (CVD), diabetes, osteoporosis and nephrotoxicity [12].

The aim of this study was to describe the prevalence of NCDs among PLHIV at the time of diagnosis, and the mortality and occurrence of NCDs over calendar time and by age compared with the background population, with a focus on the changes during the pre-, early- and late-HAART (highly active antiretroviral therapy) era.

Methods

Setting

The estimated HIV prevalence in Denmark is approximately 0.1% in the adult population. The Danish National Health Service provides free tax-funded medical care to all residents, including access to hospitals, outpatient speciality clinics and HIV medicine [17]. Denmark is divided into five administrative entities, each representative of the Danish population with respect to demographic characteristics and healthcare usage and medication use [17]. This population-based study was conducted in the Central Denmark Region with a population of approximately 1.3 million during 1985–2017. The estimated HIV prevalence in the Central Denmark Region is 0.6‰ in the adult population. In this region, PLHIV are treated in outpatient HIV clinics at Aarhus University Hospital and Regional Hospital West Jutland. We defined three eras with reference to treatment modalities: pre-HAART (1985–1996), early HAART (1996–2005), and late HAART (2006–2017).

Data sources

Since 1968 a unique personal identifier has been assigned to all residents at birth or upon immigration by the Civil Registration System (CRS) [18]. This identifier allows unambiguous data linkage at individual level. The CRS also tracks changes in vital status and migration for the entire population with daily updates. We used this personal identifier to link data from the various registries.

The Danish National Patient Registry (DNPR) includes data on all admissions to Danish hospitals since 1977, and emergency room and outpatient clinic visits since 1995. Diagnoses are classified according to the *International Classification of Diseases*, Eighth Revision (ICD-8) until 1994, and Tenth Revision (ICD-10) thereafter [19].

The InfCare HIV database is a clinical decision support tool based on the RealQ® Decision Support platform developed by Health Solutions AB, Stockholm, Sweden. Since 2010 InfCare HIV has been used at the HIV clinics in Central Denmark Region [20].

The Danish HIV Cohort Study (DHCS) is a nationwide, prospective population-based cohort that includes all HIV-infected individuals treated at Danish hospitals since 1 January 1995 [1].

Statistics Denmark's databases on municipal services contain individual-level information about weekly allocated home care and rehabilitation and training (on a yes/no basis only, without specifying the extent of the training).

The Education Register contains information about the highest level of completed education and the date of completion.

Study populations

We used data from the InfCare HIV database, DHCS and the DNPR to identify all residents of the Central Denmark Region who were 18 years or older with an HIV diagnosis first registered during 1985–2017 and who had at least one contact to one of the two HIV centres in the Central Denmark Region.

For each HIV patient we randomly selected 10 persons from the general population as a comparison cohort matched on birth year, sex and municipality of residence at time of HIV diagnosis. Comparisons could not have a known diagnosis of HIV at date of inclusion.

Non-communicable diseases at time of HIV diagnosis

We obtained information on alcohol abuse, chronic obstructive pulmonary disease (COPD), diabetes,

ischaemic heart disease (IHD), liver disease, osteoporosis, defined as a diagnosis or an osteoporotic fracture or anti-resorptive treatment, renal disease and mental disorders registered any time before the HIV diagnosis/index date for comparisons through the DNPR (see Appendix 1 for included codes). To summarize burden of comorbidity, we additionally defined comorbidity according to the Charlson Comorbidity Index (CCI) score [21]. We did not include the HIV diagnosis when computing this score. We categorized the CCI score as 0, 1 or ≥ 2. We also simply counted the number of NCDs without giving them a specific weight.

Covariates

From Statistics Denmark we obtained information on the highest obtained education before index date, grouped as primary school, secondary school, higher education and missing. We similarly obtained information on income for the year prior to the index date adjusted for inflation.

From the CRS we obtained information on country of birth and grouped persons as descending from western Europe (yes/no) (see Appendix 1 for the definition of western Europe).

Statistical analysis

We described baseline characteristics for HIV patients and their comparison cohort. Income and age were presented as median and interquartile range (IQR). We followed patients from date of initial HIV diagnosis and comparisons from index date until occurrence of NCD, death, emigration, or 31 December 2017, whichever came first. Additionally, to address the potential effect of late presenters on our estimates we conducted an analysis restricted to PLHIV who were alive 2 years after the date of HIV diagnosis by starting follow-up 2 years after that date. We estimated and plotted the cumulative incidence of death for the PLHIV and non-HIV cohorts, respectively, during the first 10 years of follow-up. We plotted the cumulative incidence of the specific NCD for PLHIV and HIV-uninfected individuals at baseline and estimated the incidence after 5 and 10 years, respectively, while treating death as a competing risk. We computed the analyses overall and stratified analyses according to age categories (< 31, 31–40, 41–50, > 51 years) and index year period and baseline CCI score.

All statistical analyses were conducted using the statistical software package SAS v.9.4 (SAS Institute, Cary, NC, USA) and the open-source statistical package R v.3.6.1.

Results

Study populations

We identified 1043 PLHIV and 10 430 HIV-uninfected comparisons who fulfilled the study population inclusion criteria. In all, 29.5% were diagnosed in the pre-HAART period, 31.4% in the early-HAART period, and 39.0% in the late-HAART period. The median (IQR) age at HIV diagnosis was 36.6 (29.3–45.5) years with 19.8% > 50 years old; 71.6% were men. Only 71.9% of PLHIV were born in western Europe compared with 93.5% of the non-HIV population. PLHIV had lower incomes and education levels compared with the non-HIV cohort, and this was also true when only data on individuals born in western Europe were analysed. PLHIV from western Europe had higher income and longer education than patients originating from other parts of the world (Tables 1 and 2).

Non-communicable diseasesn

At the time of diagnosis, the PLHIV cohort had a generally higher burden of comorbidity than the non-HIV cohort, with 14% having a CCI score ≥ 1 *vs.* 9.1% of comparisons (Tables 1 and 2). The burden of comorbidity increased with age at diagnosis, but in all age groups PLHIV had a higher burden of comorbidity, with 6.4% *vs.* 5.0% having CCI ≥ 1 in the age group < 31 years, 9.7% *vs.* 6% in the age group 31–40 years, 14.1% *vs.* 8.9% in the age group 41–50 years, and 36% *vs.* 23.7% in the age group > 51 years (Table 1).

Compared with the non-HIV cohort, PLHIV had an increased prevalence of most of the included NCDs at HIV diagnosis, such as alcohol abuse (5.4% *vs.* 2.6%), COPD (3.2% *vs.* 2.5%), IHD (1.9% *vs.* 1.5%), liver disease (3.4% *vs.* 0.6%), mental disorders (9.5% *vs.* 5.5%) and renal disease (1.2% *vs.* 0.5%), whereas there was no increase in the baseline prevalence of diabetes (1.9% vs. 2.0%) and osteoporosis (7.1% vs 8.6%) (Tables 1 and 2).

During follow-up the percentage of persons with one or more NCD increased considerably more in PLHIV than in the non-HIV cohort (Fig. 1a,b). After 10 years of follow-up, 42.2% of PLHIV had one or more registered NCDs compared with 23.9% in the non-HIV cohort, and in the age group > 51 years, 54.2% of PLHIV *vs.* 36.5% of non-HIV had at least one NCD. (Fig. 1a).

During follow-up, alcohol abuse continued to be significantly more common among PLHIV, with a 10-year cumulative incidence of 8.9% compared with 4.0% in the non-HIV cohort, and the difference was most pronounced in the oldest age group (12.6% *vs.* 6.2%) (Fig. 2a).

Table 1 Baseline characteristics of the study population stratified by age group

	Age group									
	All patients		< 31 years		31–40 years		41–50 years		> 51 years	
	Non-HIV	HIV	Non-HIV	HIV	Non-HIV	HIV	Non-HIV	HIV	Non-HIV	HIV
Total (*N*)	10 430	1043	2828	281	3457	350	2542	248	1603	164
Index year period										
1985–1995	3080 (29.5)	308 (29.5)	1162 (41.1)	115 (40.9)	1044 (30.2)	108 (30.9)	609 (24.0)	57 (23.0)	265 (16.5)	28 (17.1)
1996–2005	3280 (31.4)	328 (31.4)	801 (28.3)	81 (28.8)	1204 (34.8)	118 (33.7)	727 (28.6)	72 (29.0)	548 (34.2)	57 (34.8)
2006–2017	4070 (39.0)	407 (39.0)	865 (30.6)	85 (30.2)	1209 (35.0)	124 (35.4)	1206 (47.4)	119 (48.0)	790 (49.3)	79 (48.2)
CD4 level (cells/μL)										
Very low (< 200)	0 (0.0)	186 (17.8)	0 (0.0)	27 (9.6)	0 (0.0)	60 (17.1)	0 (0.0)	60 (24.2)	0 (0.0)	39 (23.8)
Low (200–500)	0 (0.0)	201 (19.3)	0 (0.0)	52 (18.5)	0 (0.0)	62 (17.7)	0 (0.0)	52 (21.0)	0 (0.0)	35 (21.3)
Normal (+500)	0 (0.0)	132 (12.7)	0 (0.0)	40 (14.2)	0 (0.0)	45 (12.9)	0 (0.0)	29 (11.7)	0 (0.0)	18 (11.0)
Unknown	10 430 (100.0)	524 (50.2)	2828 (100.0)	162 (57.7)	3457 (100.0)	183 (52.3)	2542 (100.0)	107 (43.1)	1603 (100.0)	72 (43.9)
Males	7470 (71.6)	747 (71.6)	1685 (59.6)	167 (59.4)	2362 (68.3)	238 (68.0)	2075 (81.6)	204 (82.3)	1348 (84.1)	138 (84.1)
Born in western Europe	9748 (93.5)	750 (71.9)	2660 (94.1)	174 (61.9)	3173 (91.8)	225 (64.3)	2376 (93.5)	197 (79.4)	1539 (96.0)	154 (93.9)
Age (years) [median (IQR)]	36.5 (29.5–45.5)	36.6 (29.3–45.5)	26.2 (23.3–28.2)	26.1 (23.4–28.3)	34.4 (32.2–37.3)	34.4 (32.1–37.3)	44.3 (42.1–46.8)	44.4 (42.0–46.7)	56.4 (52.2–62.3)	56.1 (52.0–62.3)
Income (DKK 100 000) [median (IQR)]	3.0 (2.0–4.0)	2.2 (1.3–3.3)	2.0 (1.2–2.9)	1.5 (0.7–2.2)	3.2 (2.3–4.1)	2.4 (1.3–3.4)	3.7 (2.8–4.8)	2.7 (1.7–4.0)	3.1 (2.0–4.3)	2.7 (1.9–4.1)
Highest completed education										
Primary school	2479 (23.8)	319 (30.6)	726 (25.7)	97 (34.5)	713 (20.6)	102 (29.1)	503 (19.8)	62 (25.0)	537 (33.5)	58 (35.4)
Secondary school	4956 (47.5)	406 (38.9)	1506 (53.3)	108 (38.4)	1586 (45.9)	132 (37.7)	1217 (47.9)	110 (44.4)	647 (40.4)	56 (34.1)
Higher education	2766 (26.5)	218 (20.9)	527 (18.6)	40 (14.2)	1084 (31.4)	76 (21.7)	776 (30.5)	62 (25.0)	379 (23.6)	40 (24.4)
Missing	229 (2.2)	100 (9.6)	69 (2.4)	36 (12.8)	74 (2.1)	40 (11.4)	46 (1.8)	14 (5.6)	40 (2.5)	10 (6.1)
Charlson Comorbidity Index score										
0	9474 (90.8)	897 (86.0)	2688 (95.0)	263 (93.6)	3249 (94.0)	316 (90.3)	2314 (91.0)	213 (85.9)	1223 (76.3)	105 (64.0)
1	589 (5.6)	74 (7.1)	109 (3.9)	13 (4.6)	148 (4.3)	18 (5.1)	133 (5.2)	22 (8.9)	199 (12.4)	21 (12.8)
+2	367 (3.5)	72 (6.9)	31 (1.1)	5 (1.8)	60 (1.7)	16 (4.6)	95 (3.7)	13 (5.2)	181 (11.3)	38 (23.2)
Alcohol abuse	269 (2.6)	56 (5.4)	55 (1.9)	5 (1.8)	77 (2.2)	21 (6.0)	75 (3.0)	18 (7.3)	62 (3.9)	12 (7.3)
Chronic obstructive pulmonary disease	262 (2.5)	33 (3.2)	71 (2.5)	8 (2.8)	79 (2.3)	6 (1.7)	57 (2.2)	7 (2.8)	55 (3.4)	12 (7.3)
Diabetes	212 (2.0)	20 (1.9)	21 (0.7)	N/A	38 (1.1)	N/A	64 (2.5)	N/A	89 (5.6)	N/A
Ischaemic heart disease	153 (1.5)	20 (1.9)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Liver disease	64 (0.6)	35 (3.4)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mental disorders	577 (5.5)	96 (9.2)	130 (4.6)	20 (7.1)	186 (5.4)	34 (9.7)	160 (6.3)	23 (9.3)	101 (6.3)	19 (11.6)
Renal disease	48 (0.5)	13 (1.2)	7 (0.2)	N/A	14 (0.4)	N/A	15 (0.6)	N/A	12 (0.7)	N/A
Osteoporosis/fracture	895 (8.6)	74 (7.1)	248 (8.8)	15 (5.3)	293 (8.5)	24 (6.9)	218 (8.6)	21 (8.5)	136 (8.5)	14 (8.5)
Angiotensin-converting enzyme inhibitors	222 (2.1)	26 (2.5)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Antihypertensive treatment	279 (2.7)	25 (2.4)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Angiotensin II antagonists	607 (5.8)	60 (5.8)	21 (0.7)	N/A	56 (1.6)	N/A	155 (6.1)	N/A	375 (23.4)	N/A
Oral steroids	231 (2.2)	15 (1.4)	6 (0.2)	N/A	18 (0.5)	N/A	64 (2.5)	N/A	143 (8.9)	N/A
Statins	141 (1.4)	11 (1.1)	N/A	0 (0.0)	N/A	0 (0.0)	N/A	6 (2.4)	N/A	5 (3.0)
Thrombocyte-aggregation prophylaxis	202 (1.9)	33 (3.2)	33 (1.2)	0 (0.0)	55 (1.6)	9 (2.6)	60 (2.4)	12 (4.8)	54 (3.4)	12 (7.3)

IQR, interquartile range.

Table 2 Baseline characteristics of the study population stratified by index year period

	Index year period							
	All patients		1985–1995		1996–2005		2006–2017	
	Non-HIV	HIV	Non-HIV	HIV	Non-HIV	HIV	Non-HIV	HIV
Total (*N*)	10 430	1043	3080	308	3280	328	4070	407
Age group (years)								
< 31	2828 (27.1)	281 (26.9)	1162 (37.7)	115 (37.3)	801 (24.4)	81 (24.7)	865 (21.3)	85 (20.9)
31–40	3457 (33.1)	350 (33.6)	1044 (33.9)	108 (35.1)	1204 (36.7)	118 (36.0)	1209 (29.7)	124 (30.5)
41–50	2542 (24.4)	248 (23.8)	609 (19.8)	57 (18.5)	727 (22.2)	72 (22.0)	1206 (29.6)	119 (29.2)
> 51	1603 (15.4)	164 (15.7)	265 (8.6)	28 (9.1)	548 (16.7)	57 (17.4)	790 (19.4)	79 (19.4)
CD4 level (cells/μL)				N/A		N/A		N/A
Very low (< 200)	0 (0.0)	186 (17.8)	0 (0.0)	N/A	0 (0.0)	N/A	0 (0.0)	N/A
Low (200–500)	0 (0.0)	201 (19.3)	0 (0.0)	N/A	0 (0.0)	N/A	0 (0.0)	N/A
Normal (+500)	0 (0.0)	132 (12.7)	0 (0.0)	N/A	0 (0.0)	N/A	0 (0.0)	N/A
Unknown	10 430 (100.0)	524 (50.2)	3080 (100.0)	N/A	3280 (100.0)	N/A	4070 (100.0)	N/A
Males	7470 (71.6)	747 (71.6)	2350 (76.3)	235 (76.3)	2220 (67.7)	222 (67.7)	2900 (71.3)	290 (71.3)
Born in western Europe	9748 (93.5)	750 (71.9)	2971 (96.5)	261 (84.7)	3083 (94.0)	216 (65.9)	3694 (90.8)	273 (67.1)
Age (years) [median (IQR)]	36.5 (29.5–45.5)	36.6 (29.3–45.5)	33.0 (27.3–41.7)	33.0 (27.3–41.5)	37.4 (30.1–44.7)	37.2 (30.2–44.8)	39.3 (31.2–47.7)	39.5 (31.2–47.7)
Income (DKK 100 000) [median (IQR)]	3.0 (2.0–4.0)	2.2 (1.3–3.3)	2.9 (1.9–3.8)	2.2 (1.3–3.2)	3.0 (2.0–3.9)	2.1 (1.2–3.2)	3.2 (2.1–4.3)	2.4 (1.3–3.6)
Highest completed education								
Primary school	2479 (23.8)	319 (30.6)	831 (27.0)	93 (30.2)	812 (24.8)	104 (31.7)	836 (20.5)	122 (30.0)
Secondary school	4956 (47.5)	406 (38.9)	1544 (50.1)	130 (42.2)	1558 (47.5)	135 (41.2)	1854 (45.6)	141 (34.6)
Higher education	2766 (26.5)	218 (20.9)	637 (20.7)	51 (16.6)	847 (25.8)	72 (22.0)	1282 (31.5)	95 (23.3)
Missing	229 (2.2)	100 (9.6)	68 (2.2)	34 (11.0)	63 (1.9)	17 (5.2)	98 (2.4)	49 (12.0)
Charlson Comorbidity Index score								
0	9474 (90.8)	897 (86.0)	2956 (96.0)	273 (88.6)	3022 (92.1)	289 (88.1)	3496 (85.9)	335 (82.3)
1	589 (5.6)	74 (7.1)	77 (2.5)	17 (5.5)	166 (5.1)	23 (7.0)	346 (8.5)	34 (8.4)
+2	367 (3.5)	72 (6.9)	47 (1.5)	18 (5.8)	92 (2.8)	16 (4.9)	228 (5.6)	38 (9.3)
Alcohol abuse	269 (2.6)	56 (5.4)	46 (1.5)	13 (4.2)	83 (2.5)	19 (5.8)	140 (3.4)	24 (5.9)
Chronic obstructive pulmonary disease	262 (2.5)	33 (3.2)	26 (0.8)	6 (1.9)	72 (2.2)	13 (4.0)	164 (4.0)	14 (3.4)
Diabetes	212 (2.0)	20 (1.9)	22 (0.7)	N/A	45 (1.4)	N/A	145 (3.6)	N/A
Ischaemic heart disease	153 (1.5)	20 (1.9)	11 (0.4)	N/A	34 (1.0)	N/A	108 (2.7)	N/A
Liver disease	64 (0.6)	35 (3.4)	11 (0.4)	13 (4.2)	15 (0.5)	9 (2.7)	38 (0.9)	13 (3.2)
Mental disorders	577 (5.5)	96 (9.2)	111 (3.6)	26 (8.4)	171 (5.2)	29 (8.8)	295 (7.2)	41 (10.1)
Renal disease	48 (0.5)	13 (1.2)	8 (0.3)	N/A	18 (0.5)	N/A	22 (0.5)	N/A
Osteoporosis/fracture	895 (8.6)	74 (7.1)	100 (3.2)	12 (3.9)	254 (7.7)	20 (6.1)	541 (13.3)	42 (10.3)
Angiotensin-converting enzyme inhibitors	222 (2.1)	26 (2.5)	N/A	N/A	N/A	N/A	N/A	N/A
Antihypertensive treatment	279 (2.7)	25 (2.4)	0 (0.0)	N/A	30 (0.9)	N/A	249 (6.1)	N/A
Angiotensin II antagonists	607 (5.8)	60 (5.8)	6 (0.2)	0 (0.0)	189 (5.8)	22 (6.7)	412 (10.1)	38 (9.3)
Oral steroids	231 (2.2)	15 (1.4)	N/A	0 (0.0)	N/A	0 (0.0)	N/A	15 (3.7)
Statins	141 (1.4)	11 (1.1)	0 (0.0)	N/A	30 (0.9)	N/A	111 (2.7)	N/A
Thrombocyte-aggregation prophylaxis	202 (1.9)	33 (3.2)	N/A	N/A	N/A	N/A	N/A	N/A

IQR, interquartile range.

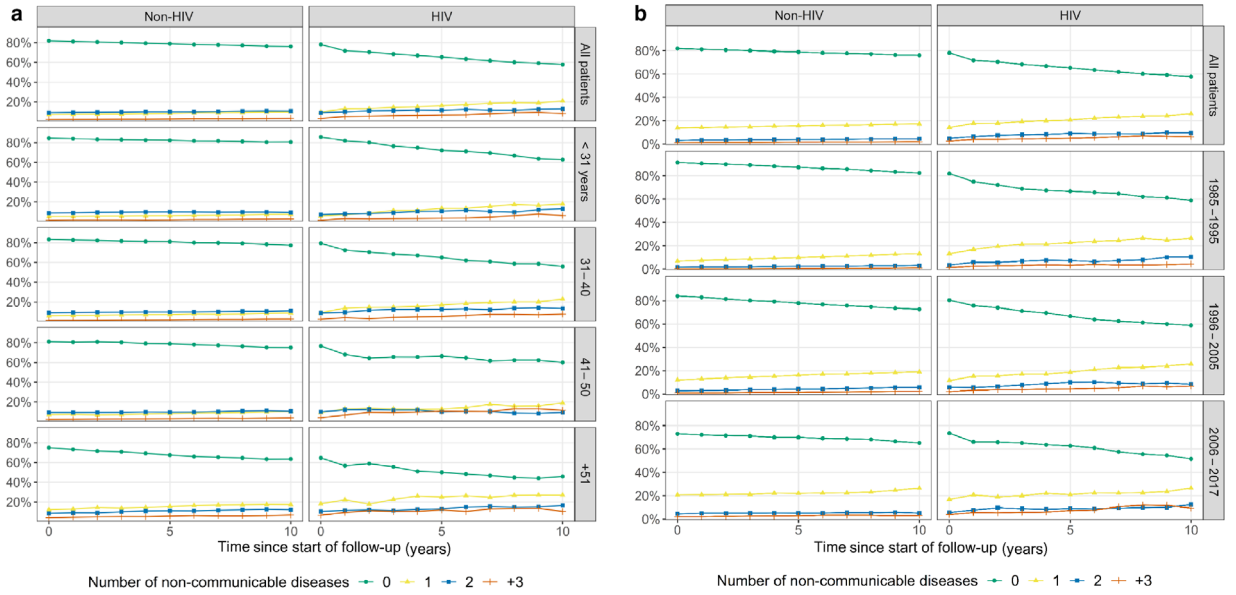

Fig. 1 (a) Distribution of number of non-communicable diseases within 10 years after the date of HIV diagnosis, stratified by age groups. (b) Distribution of number of non-communicable diseases within 10 years after the date of HIV diagnosis, stratified by index period into pre-HAART (highly active antiretroviral therapy) (1985–1995), early-HAART (1996–2005) and late-HAART (2006–2017) eras. [Colour figure can be viewed at wileyonlinelibrary.com]

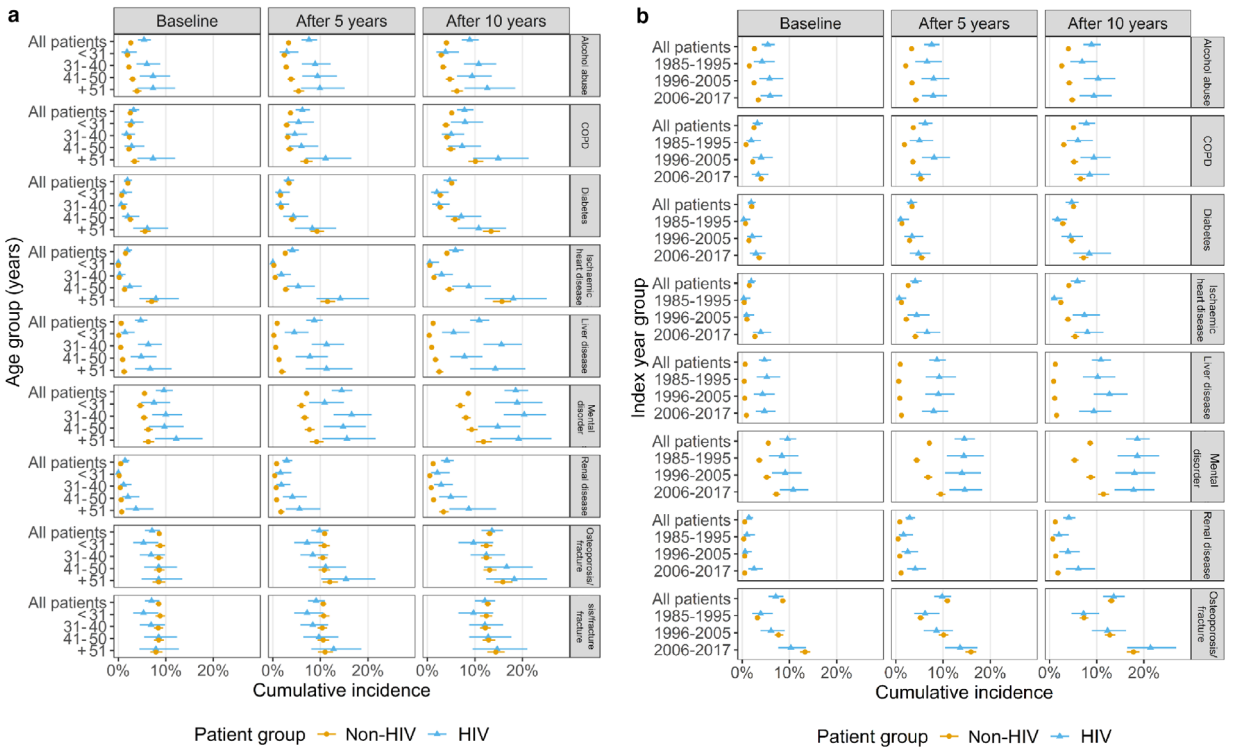

Fig. 2 (a) Baseline prevalence and 5- and 10-year cumulative incidence of non-communicable diseases stratified by age groups. (b) Baseline prevalence and 5- and 10-year cumulative incidence of non-communicable diseases stratified by index period into pre-HAART (highly active antiretroviral therapy) (1985–1995), early-HAART (1996–2005), and late HAART (2006–2017) eras. COPD, chronic obstructive pulmonary disease. [Colour figure can be viewed at wileyonlinelibrary.com]

The prevalence of mental disorders during follow-up increased in PLHIV from 9.6% to 18.6%, which was much higher than in the non-HIV cohort (increase from 5.5% to 8.6%) (Fig. 2a,b).

People living with HIV also had a slightly higher cumulative incidence of COPD, increasing from 3.2% at baseline to 7.8% after 10 years' follow-up compared with 2.5% and 5.1%, respectively, in the non-HIV cohort. In the age group > 51 years, the cumulative incidences after 10 years were 14.9% and 10.1% in the PLHIV and the non-HIV cohorts, respectively (Fig. 2a,b). In the late-HAART era, no increased prevalence of COPD was observed (Fig. 2b).

Whereas the cumulative incidence of liver disease during follow-up only increased from 0.6% to 1.2% in the non-HIV cohort, it increased from 4.7% to 10.9% among PLHIV (Fig. 2a,b). This shows that PLHIV had a much higher prevalence and incidence of liver disease than HIV-uninfected individuals, independent of index year but increasing with age (Fig. 2a,b).

Renal disease was also more prevalent among PLHIV, with a 10-year cumulative incidence of 4.1% compared with 1.2% in the non-HIV cohort, and 8.7% and 3.4% in the > 51years age group, respectively. The 10-year cumulative incidence was higher in the late-HAART (6.1%) compared with the early- (3.9%) and pre-HAART eras (2.0%) (Fig. 2a,b).

There were no major differences in the cumulative incidences of diabetes and IHD between PLHIV and the non-HIV cohort. In the > 51-year age group, the 10-year cumulative incidence for diabetes was 10.8% *vs.* 13.4% and for IHD it was 18.1% *vs.* 15.7% in the HIV and non-HIV cohorts, respectively. However, the prevalence rates of diabetes and IHD were higher in both groups during the late-HAART era than during the pre-HAART era (Fig. 2a,b).

Overall, the cumulative incidence of osteoporosis did not differ between the HIV and the non-HIV groups. The prevalence of osteoporosis increased with age, and in the age groups 41–50 and > 51 years, PLHIV had higher cumulative incidences of osteoporosis, being 18.3% and 16.7%, respectively, after 10 years of follow-up compared with 15.9% and 13.1% in the non-HIV group (Fig. 2a,b). The 10-year cumulative incidence of osteoporosis was higher in the late-HAART (21.4%) than in the early- (12.3%) and pre-HAART eras (7.2%) (Fig. 2a,b). Osteoporotic fractures accounted for 99% of all the osteoporosis diagnoses and suggested no difference between calendar periods.

Mortality

Overall, 10-year mortality was 23.0% for PLHIV *vs.* 3.5% in the non-HIV cohort, but it improved considerably over time (Fig. 3a). The 10-year mortality rates of those in the two cohorts who were alive 2 years after the date of HIV diagnosis were 15.2% for PLHIV *vs.* 3.9% in the non-HIV cohort, whereas the mortality of PLHIV who were alive 2

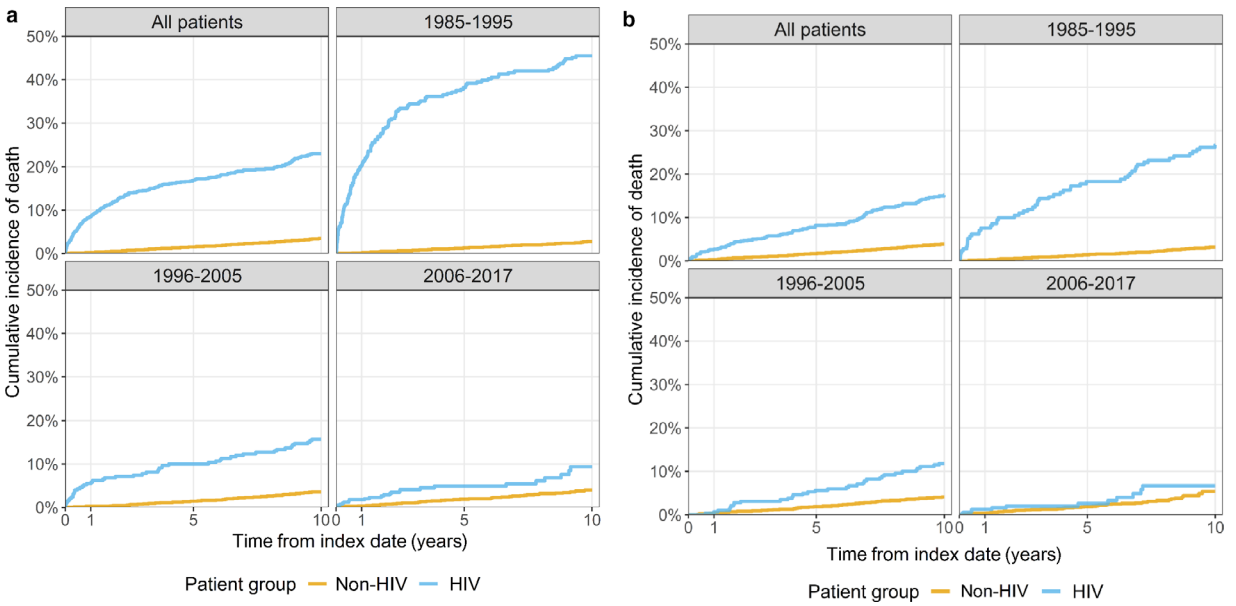

Fig. 3 (a) Cumulative all-cause mortality, stratified by index year period, pre-HAART (highly active antiretroviral therapy) (1985–1995), early-HAART (1996–2005) and late-HAART (2006–2017) eras. (b) Cumulative all-cause mortality from 2 years after the date of HIV diagnosis/index date, stratified by index year period, pre-HAART (1985–1995), early-HAART (1996–2005) and late-HAART (2006–2017) eras. [Colour figure can be viewed at wileyonlinelibrary.com]

years after the HIV diagnosis date in the late-HAART era resembled that of the uninfected population in the same era (Fig. 3b). In the pre-, early- and late-HAART eras, mortality rates in the first year after HIV diagnosis were 20.3%, 5.5% and 1.8%, respectively, and 10-year mortality rates were 45.5%, 15.7% and 9.4%. In the non-HIV cohort, the 10-year mortality rates were 2.8%, 3.6% and 4.0% in the three respective HAART eras.

Assessing the relationship between the prevalence of comorbidities and mortality, for PLHIV with a CCI score ≥ 2, the 5- and 10-year mortality rates were 30.8% and 40.7%, respectively, compared with 15.9% and 21.3% for those without comorbidity.

Discussion

This population-based study with long-term follow-up confirms that PLHIV have a higher prevalence of NCD at the time of their HIV diagnosis than age- and sex-matched members of the background population, but also a disproportionate risk of NCD during follow-up, not least in the late-HAART era when PLHIV mortality had substantially decreased. Thus, despite a dramatic reduction in mortality over calendar time, PLHIV continue to have a higher mortality compared with the background population. However, the mortality of PLHIV who survived the first 2 years after the date of HIV diagnosis in the late-HAART era was close to that of the general population in the same era. Danish studies have shown that one-third of PLHIV present with advanced HIV infection [22,23]. One study found that 34.7% presented with advanced HIV and 51.2% of individuals diagnosed with HIV were late presenters. Among others, the risk of presenting with advanced HIV was associated with age > 50 years, and mortality rates were increased during the first 2 years following presentation with advanced HIV [23]. Thus, the increased mortality among PLHIV may be caused by AIDS-related deaths among late presenters during the first year after diagnosis and a disproportionate burden of NCDs during follow-up. Not surprisingly, comorbidities are associated with an increased mortality. Although many PLHIV were probably infected several years before the date of diagnosis, the higher prevalence of NCDs at the time of diagnosis may be explained, at least partly, by lower socioeconomic status and unhealthy lifestyle such as smoking and alcohol abuse among PLHIV.

Exposure to antiretroviral drugs has been associated with hyperglycaemia and ART-exposed PLHIV have been found to have an increased risk of diabetes [24,25]. However, we did not find an increased risk of diabetes among PLHIV during the first 10 years after HIV diagnosis, not even in the early-HAART period where first-generation protease inhibitors were in use. This is in line with findings from a previous Danish study that the risk of diabetes in PLHIV was only increased in the period 1996–1999 but not 1999–2010 [26]. In accordance with the global trend, the prevalence of diabetes increased from the pre- to the late-HAART era among PLHIV and HIV-uninfected individuals.

HIV infection has been associated with an almost two-fold increase in the incidence of IHD, and CVD is one of the most frequent causes of death among HIV-infected individuals [27,28]. This may be linked to a high prevalence of risk factors for CVD, such as smoking, hypertension and dyslipidaemia in PLHIV [9,28]. Smoking is associated with higher risk of myocardial infarction (MI) in PLHIV than in the background population and up to 70% of MI in PLHIV may be attributable to smoking [29]. Initiation of ART has also been associated with an increased incidence of MI [30]. In particular, abacavir-based regiments are linked to a nearly two-fold increase in the risk of MI [31]. In addition, immune activation may increase the risk of MI [27]. Still, we only found a slightly higher prevalence of IHD at baseline and during follow-up. In agreement with this, a recent Australian study including HIV-infected and non-HIV-infected men attending general practice found no difference in the prevalence of CVD (9.4% *vs*. 9.6%) [8]. In a German HIV cohort, the prevalence of CVD was 12.8% *vs*. 10.4% in a non-HIV cohort matched on age, gender and socioeconomic variables, similar to our findings [32].

Respiratory symptoms are common among PLHIV, and COPD may present earlier and be more severe than in the general population [33]. The global prevalence of COPD among PLHIV is 5.6–10.6%, the highest in Europe and among smokers, but it varies considerably among different HIV cohorts [34]. Consistently, we found a higher cumulative incidence of COPD among PLHIV compared with the non-HIV group, most probably explained by higher prevalence of smoking as studies have shown that the prevalence of smoking among PLHIV is two to three times that of the general population [12]. However, previous findings also suggested that PLHIV have a higher prevalence of COPD even after adjusting for smoking [35]. The pathogenesis of HIV-related lung disease, independent of smoking, is not fully understood, but altered lung microbiome and chronic inflammation caused by residual HIV have been proposed [35]. Still, tobacco use remains an important modifiable risk factor for COPD.

Chronic kidney disease (CKD) is a common complication of HIV infection, but the spectrum has changed since the beginning of the epidemic. HIV-associated nephropathy was frequent before the availability of ART [36,37]. Nowadays, CKD is primarily associated with ART and traditional risk factors such as ageing, hypertension, diabetes,

dyslipidaemia and smoking [36,37]. In accordance with our study, the prevalence of CKD among PLHIV has been found to be 2–10% but varies across populations [36–38]. Further, HIV-infected individuals have a two to 20 times higher risk of developing end-stage renal disease compared with the background population [39]. Our study confirms a two- to four-fold increased incidence of renal disease in PLHIV compared with the non-HIV group during follow-up. Rasmussen *et al.* [40] showed that the age-standardized risk of CKD increased with calendar years. In accordance with our findings, the cumulative incidence of CKD was higher in the late-HAART era. This indicates that CKD may be attributable primarily to an increased use of potential nephrotoxic antiretrovirals. Several antiretrovirals such as indinavir, atazanavir and tenofovir disoproxil fumarate (TDF) are associated with impairment of renal function [36,37,41].

In the post-HAART era, liver disease has become a leading cause of morbidity and mortality in PLHIV [5,6,29]. Elevated liver transaminases have been reported in 20–93% of PLHIV on ART [40]. PLHIV have higher prevalence of several risk factors for liver damage, such as alcohol abuse, coinfection with hepatitis B and C viruses due to shared risk factors, hepatotoxicity associated with ART, HIV itself, and metabolic dysfunction leading to non-alcoholic fatty liver disease (NAFLD) [42–44]. Based on alcohol-related hospital diagnoses, our study confirms that alcohol abuse is twice as common among PLHIV than among the general population and increasing during follow-up. In line with our data, studies have found that 8–11% of PLHIV are heavy drinkers [45–47]. In accordance with previous studies, liver disease was approximately eight times more prevalent in the PLHIV group than in the non-HIV group. In the DHCS, 10% were infected by intravenous drug use (IDU) and 13% were HCV-positive [46]. In a previous survey among 574 PLHIV living in the Central Denmark Region, only 3% had chronic hepatitis B and 4% had chronic hepatitis C [48]. Thus, the increased cumulative incidence of liver disease among PLHIV cannot be solely explained by chronic viral hepatitis. Hepatotoxicity is a common side-effect associated with ART, especially with some of the older drugs, and may be an important contributor to liver disease [42,43]. However, metabolic liver diseases have become increasingly common among PLHIV and recent studies have identified NAFLD as the most common cause of liver disease in individuals ageing with HIV mono-infection [42,47].

People living with HIV have been found to have an increased risk of osteoporosis and fractures compared with HIV-uninfected individuals of the same age and sex [49,50]. This may be a result of traditional risk factors or factors intrinsic to HIV. Initiation of ART is associated with bone loss, especially regimens that include TDF [49]. A recent systematic review and meta-analysis found an approximately 50% increased risk of any fracture [50]. In this study, only PLHIV in the age groups 41–50 and > 51 years had a higher incidence of osteoporosis compared with the background population. Similarly, in a study from the Multicenter AIDS Cohort Study only HIV-positive men aged 50–59 years had a higher incidence of all fractures [51]. The prevalence of osteoporosis increased with age and over calendar time and was considerably higher in the late-HAART era than in the pre-HAART era. This cannot be solely explained by ART toxicity as a similar increase was seen in the non-HIV group. Current guidelines for PLHIV recommend using a bone density scan (DXA) for screening for osteoporosis in postmenopausal women and men aged > 50 years [49]. This was not implemented in the study period, and therefore osteoporosis may be underdiagnosed in our cohort.

The prevalence of mental disorders in our PLHIV was approximately twice as high as in the non-HIV group. This may partly be explained by IDU being associated with psychiatric disorders and having an increased risk of HIV infection. However, HIV-infected persons with no history of IDU or HCV infection have been shown to have a higher utilization of psychotropic drugs [52]. Further, the prevalence of depression is two to seven times higher in the HIV population than in the background population [53]. Thus, it may work both ways. Mental disorders may increase the risk of acquiring HIV, and HIV infection may cause mental disorders. As mental disorders may be associated with poor adherence to ART, it is important that HIV care addresses this problem.

The strengths of our study are the use of a region-wide, population-based cohort with long and complete follow-up and the access to high-quality Danish population-based databases, which allowed us to construct an age- and sex-matched comparison cohort to represent occurrence of NCDs in the general population. The study has limitations. Our HIV cohort was not matched on socioeconomic status, ethnicity or marital status. We lacked information on lifestyle factors such as smoking and IDU, antiretroviral exposure and CD4 cell count, so we could not examine how the occurrence of NCDs varied by these factors. Therefore, we also kept our study descriptive and avoided any formal comparison with the general population cohort. Due to the retrospective design of the study, 10-year follow-up data were available for only 754 (16.8%) individuals in the late-HAART era compared with 2996 (88.4%) and 3282 (91%) individuals in the pre- and early-HAART eras, respectively. Another weakness is that we relied on hospital diagnoses when identifying NCDs and alcohol abuse and we missed

diagnoses from general practitioners. As PLHIV have regular contact with the healthcare system, this may lead to a higher proportion of diagnoses actually recorded in a hospital setting as the matched population cohort only had information on alcohol abuse and diagnoses if they had been in contact with the healthcare system. Still, Denmark has a uniform and equal healthcare system with free access to hospital treatment for acute diseases. We therefore expect such potential surveillance bias to be minor for severe diseases like IHD. Further, we did not have information on NCDs diagnosed before immigration to Denmark. As a higher proportion of PLHIV were born outside Denmark, we may have less complete information on prevalent NCDs in the group and subsequently overestimate the cumulative incidence of NCDs occurring after HIV diagnosis. We have no information on causes of death, but several studies have shown that excess mortality among well-treated HIV-infected individuals is primarily caused by age-related NCD [5,6,29].

In conclusion, PLHIV treated with modern and effective ART continue to have excess mortality. This may be attributable to a disproportionate burden of NCDs. We find that PLHIV have an increased risk of alcohol abuse, COPD, IHD, liver disease, mental disorders and renal disease, but not diabetes. An increased incidence of osteoporosis was only observed in PLHIV in the age groups 41–50 and > 51 years. Not surprisingly, the burden of NCDs increased with increasing age. Our data also indicate that the burden of diabetes, IHD, osteoporosis and renal disease has increased over calendar time, being at its highest in the late-HAART era.

With an ageing HIV population, improvement of survival and quality of life among PLHIV needs screening for and prevention of age-related NCDs, including lifestyle changes and use of ART with minimal toxicity.

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Author contributions

CSL, MN, FA and JD contributed to the design and the protocol of the study. NAJ implemented the study, supervised by CSL. MN performed the analyses. NAJ, CSL and MN drafted the manuscript. All authors discussed the results and contributed to the final manuscript.

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Appendix 1: Codes used for the analyses

Disease	Included ICD-8 and ICD-10 codes[1]	Included ATC codes	Included surgery codes
HIV	07983, Y4049, Y4149, DB20, DB21, DB22, DB23, DB24, DF024, DO987	NA	NA
Alcohol abuse	291, 303, 57109, 57110, 57710, 979, 980, DF10, DG312, DG21, DG721, DI426, DK292, , DK860, DK70, DR780, DF10, DG312, DG621, DG721, DI426, DK292, DK860, DK70, DR780, DT51, DZ714, DZ721	NA	NA
Chronic obstructive pulmonary disease	490, 491, 492, 493, 515, 516, 517, 518, DJ40, DJ41, DJ42, DJ43, DJ44, DJ45, DJ46, DJ47, DJ60, DJ61, DJ62, DJ63, DJ64, DJ65, DJ66, DJ67, DJ684, DJ701, DJ703, DJ841, DJ920, DJ961, DJ982, DJ983	NA	NA
Diabetes	24900, 24906, 24907, 24909, 25000, 25006, 25007, 25009, 24901, 24902, 24903, 24904, 24905, 24908, 25001, 25002, 25003, 25004, 25005, 25008, DE100, DE101, DE109, DE110, DE111, DE119, DE102, DE103, DE104, DE105, DE106, DE107, DE108, DE112, DE113, DE114, DE115, DE116, DE117, DE118	A10A, A10B	NA
Ischaemic heart disease	410, 411, 412, 413, 414, 415, DI20, DI21, DI22, DI23, DI24, DI25, DC88, DT822A, DT823	NA	KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNG, KFNH, KFNW, KFLF
Liver disease	571, 57301, 57304, 07000, 07002, 07004, 07006, 07008, 57300, 4560, DB18, DK700, DK701, DK702, DK703, DK709, DK71, DK73, DK74, DK760, DB150, DB160, DB162, DB190, DK704, DK72, DK766, DI85	NA	NA
Mental disorders	29, 30, 30, 31, 32, 33, 34, DF	N05A, N05BA, N05CD, N05CF, N06A	NA
Osteoporosis	723.09 805-809, 810-818, 820-821, DM485, DM80-M82, DS12 , DS22.0, DS22.1, DT08, DS32, DS42.2, DS42.3, DS42.4, DS42.7, DS42.8, DS52, DS62, DS72	G03XC, H05A, H05B, M05BA, M05BB, M05BX	NA
Renal disease	403, 404, 580, 581, 582, 583, 584, 59009, 59319, 7531, 792, DI12, DI13, DN00, DN01, DN02, DN03, DN04, DN05, DN07, DN11, DN14, DN17, DN18, DN19, DQ61	NA	NA

[1]International Classification of Diseases-10 (ICD-10) codes are given as SKS codes, i.e. they have a 'D' prefix

Appendix 1 (*Continued*)

Medication	Included ATC codes
Thrombocyte-aggregation prophylaxis	B01AC06, N02BA01, B01AC30, B01AC07, B01AC22, B01AC04, B01AC24
Statins	C10AA, C10BA, C10BX
Antihypertensive treatment	C01, C02, C03A, C03B, C03D, C03E, C07, C08, C09A, C09B, C09C, C09D, C09X
Angiotensin-converting enzyme inhibitors	C09A, C09B
Angiotensin II receptor blockers	C09C, C09D
Oral corticosteroids	H02AB

Charlson Comorbidity Index disease categories	Included ICD-8 and ICD-10 codes[1]
Myocardial infarction	410, DI21, DI22, DI23
Congestive heart failure	42709, 42710, 42711, 42719, 42899, 78249, DI50, DI110, DI130, DI132
Peripheral vascular disease	440, 441, 442, 443, 444, 445, DI70, DI71, DI72, DI73, DI74, DI77
Cerebrovascular disease	430, 431, 432, 433, 434, 435, 436, 437, 438, DI6, DG45, DG46
Dementia	29009, 2901, 29309, DF00, DF01, DF02, DF03, DF051, DG30
Chronic pulmonary disease	490, 491, 492, 493, 515, 516, 517, 518, DJ40, DJ41, DJ42, DJ43, DJ44, DJ45, DJ46, DJ47, DJ60, DJ61, DJ62, DJ63, DJ64, DJ65, DJ66, DJ67, DJ684, DJ701, DJ703, DJ841, DJ920, DJ961, DJ982, DJ983
Connective tissue disease	712, 716, 734, 446, 13599, DM05, DM06, DM08, DM09, DM30, DM31, DM32, DM33, DM34, DM35, DM36, DD86
Ulcer disease	53091, 53098, 531, 532, 533, 534, DK221, DK25, DK26, DK27, DK28
Mild liver disease	571, 57301, 57304, DB18, DK700, DK701, DK702, DK703, DK709, DK71, DK73, DK74, DK760
Diabetes without end-organ damage	24900, 24906, 24907, 24909, 25000, 25006, 25007, 25009, DE100, DE101, DE109, DE110, DE111, DE119
Hemiplegia	344, DG81, DG82
Moderate to severe renal disease	403, 404, 580, 581, 582, 583, 584, 59009, 59319, 7531, 792, DI12, DI13, DN00, DN01, DN02, DN03, DN04, DN05, DN07, DN11, DN14, DN17, DN18, DN19, DQ61
Diabetes with end-organ damage	24901, 24902, 24903, 24904, 24905, 24908, 25001, 25002, 25003, 25004, 25005, 25008, DE102, DE103, DE104, DE105, DE106, DE107, DE108, DE112, DE113, DE114, DE115, DE116, DE117, DE118
Non-metastatic solid tumour	14, 15, 16, 17, 18, 190, 191, 192, 193, 194, DC0, DC1, DC2, DC3, DC4, DC5, DC6, DC70, DC71, DC72, DC73, DC74, DC75
Leukaemia	204, 205, 206, 207, DC91, DC92, DC93, DC94, DC95
Lymphoma	200, 201, 202, 203, 27559, DC81, DC82, DC83, DC84, DC85, DC88, DC90, DC96
Moderate to severe liver disease	07000, 07002, 07004, 07006, 07008, 57300, 4560, DB150, DB160, DB162, DB190, DK704, DK72, DK766, DI85
Metastatic solid tumour	195, 196, 197, 198, 199, DC76, DC77, DC78, DC79, DC80
AIDS	07983, DB21, DB22, DB23, DB24

[1] International Classification of Diseases-10 (ICD-10) codes are given as SKS codes, i.e. they have a 'D' prefix

The definition of western Europe included the following countries

Austria, Belgium, Denmark, Faroe Islands, Finland, France, Germany, Greenland, Iceland, Ireland, Italy, Liechtenstein, Luxembourg, Monaco, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom.