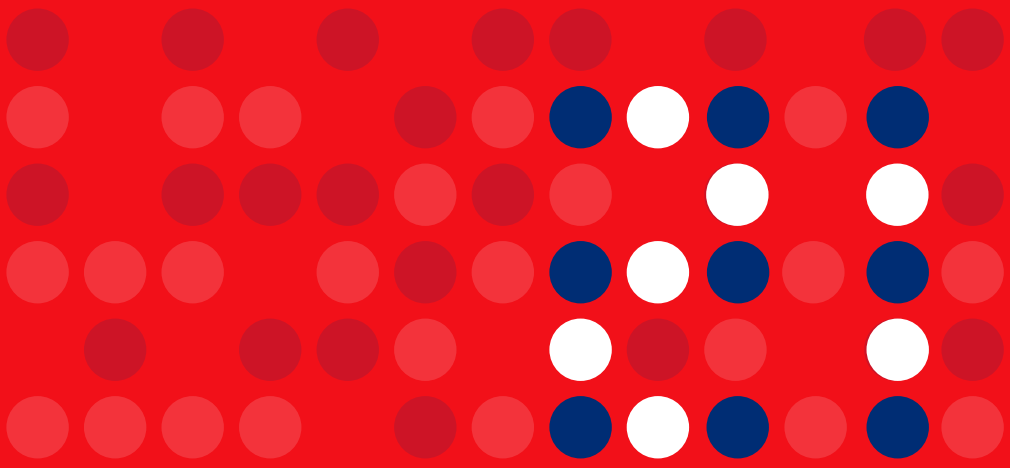
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring Report 2021

Chapter 3: Morbidity and mortality



3. Morbidity and mortality

Ferdinand Wit, Berend van Welzen, Marc van der Valk

Introduction

Since the introduction of combination antiretroviral therapy (cART) in 1996, the life expectancy of HIV-1-positive individuals has markedly improved; in a subgroup of recently-diagnosed, effectively-treated individuals, it was shown to be similar to that of the general population in the Netherlands[1]. Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased[2], morbidity and/or mortality associated with non-AIDS-related diseases has increased among HIV-1-positive individuals during the cART era[3-8]; for example, renal and liver disease, diabetes mellitus, myocardial infarction, stroke, osteoporosis, and non-AIDS-defining malignancies.

Various reports suggest that the risk of non-AIDS morbidity may be higher in individuals living with HIV treated with antiretroviral therapy (ART), than in HIV-negative individuals of comparable age[9-11]. For example, pulmonary hypertension[12], bone disease, and non-traumatic bone fractures[13-15], have each been reported to be more common in HIV-1-positive individuals. There is also a concern that HIV-related neurocognitive impairment may persist, or even progress, despite otherwise effective long-term cART[16-18]. Just as with HIV-negative individuals, traditional risk factors (e.g., tobacco use[19], alcohol abuse, and viral hepatitis co-infection[20]), also contribute to the increased risk of certain non-AIDS comorbidities in people living with HIV.

One of the most prevalent comorbidities is cardiovascular disease (CVD). In addition to traditional risk factors such as smoking, probable additional risk factors with high prevalence among HIV-1-positive individuals include metabolic abnormalities, such as dyslipidaemia; insulin resistance; hypertension; diabetes; and changes in body composition, which may be driven partly by the use of cART, as well as by sustained, residual HIV-associated immune activation and inflammation, despite effective cART[21,22].

In this chapter, we report on mortality and its causes for HIV-1-positive adults (18 years and older) using updated stichting hiv monitoring (SHM) data. We look at a total of 28,240 adult individuals ever registered by SHM – that breaks down as 27,760 adults and an additional 479 individuals who were diagnosed with HIV as children and have since become adults. In addition, we report on the incidence of AIDS and non-AIDS comorbidities, particularly diabetes mellitus, cardiovascular disease, chronic kidney disease (CKD), and non-AIDS malignancies in HIV-1-positive individuals.

Definitions

AIDS is defined as having experienced any of the United States' Centers for Disease Control (CDC) category C conditions[23]. In contrast to what is usual in the US, in our analyses, a CD4 count below 200 cells/mm^3 in the absence of an AIDS-defining condition, does not qualify as AIDS.

The following are defined according to criteria established by the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study: diabetes mellitus; CVD (including myocardial infarction, stroke, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy); and non-AIDS-defining malignancies (excluding precancerous stages of anal and cervical cancer, basal cell carcinoma, and squamous cell carcinoma of the skin). In addition, Castleman's disease is also considered a non-AIDS-defining malignancy.

Histological confirmation of malignancies is part of standard clinical practice in the Netherlands. As a result, pathology reports, wherever possible, have been used to establish the presence of any malignancy.

Chronic kidney disease (CKD) is defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min (estimated with the Cockcroft-Gault equation), confirmed after six months or longer. In previous Monitoring Reports, we used a period of three months, but in the present Monitoring Report, we have extended the period to six months because of the large number of episodes of renal dysfunction that revert shortly after three months, and which do not represent true CKD.

Methods

For the analyses of incidence per calendar year and calendar period, we have considered all events after an individual entered care following HIV-1 diagnosis, or after the start of routine collection of data on the condition of interest, whichever was most recent. For instance, data on CKD were analysed from April 2007 onwards, because that was when routinely-collected renal laboratory data became available for analysis. As the average age of the Dutch HIV population has increased over time, we also estimated the incidence rates for the periods 2000-10, 2011-15, and 2016-20. We standardised these estimates according to the age distribution of the population during the period 2016-20 (divided into the following age classes: 18-29, 30-39, 40-49, 50-59, 60-69, and 70 years or older), using the indirect method[24]. Indirect standardisation compares the incidence rates in the study and reference (period: 2016-20) populations by applying the stratum-specific rates in the reference population to the study population. We investigated risk factors for AIDS, death, and each of the non-AIDS events, as well as a combined non-AIDS endpoint

(defined as first occurrence of cardiovascular disease, diabetes mellitus, or non-AIDS-defining malignancy). CKD was not included in this combined endpoint as serum creatinine was not part of routine data collection before 2007.

The baseline for treated and untreated HIV-1-positive individuals was defined as the date of HIV-1 diagnosis or January 2000, whichever was most recent. Subsequent follow-up time was divided into periods of three months. Poisson regression models were used to estimate the independent association between risk factors and each endpoint. Models were adjusted for the most recent CD4 cell count (lagged by three months), body mass index, gender, region of birth, most likely mode of HIV-1 transmission, current age, having started cART within 12 months of the last negative HIV test, known time spent with CD4 count below 200 cells/mm^3, known time spent with plasma HIV RNA above 1,000 copies/ml while on cART, time on cART, specific antiretroviral drugs used, prior diagnosis of AIDS, presence of chronic active hepatitis B and/or C virus infection, hypertension, smoking, and calendar period.

Mortality

Mortality was investigated in all 28,240 HIV-1-positive adults ever registered in the SHM database. The mortality rate was 18.2 (95% confidence interval [CI] 13.5-23.9) per 1,000 person years of follow up (PYFU) in 1996, and declined to 8.9 (95% CI 7.4-10.5) per 1,000 PYFU in 2010. It has since remained stable at that 2010 level with an observed mortality rate of 9.0 (95% CI 7.7-10.5) in 2020 (*Figure 3.1A*). Despite this improvement over time, the mortality rate in HIV-1-positive adults remained well above the age-matched and gender-matched mortality observed in the general population in the Netherlands, which was 5.0 per 1,000 PYFU in 2020. This excess mortality can be only partly ascribed to individuals who already had AIDS at the time of their HIV diagnosis, even less so in recent years. When these individuals were excluded from the analysis, the mortality rate decreased from 14.1 (95% CI 9.8-19.6) per 1,000 PYFU in 1996 to 8.2 (95% CI 6.8-9.7) per 1,000 PYFU in 2020, still well above the observed mortality rates in the age-matched and gender-matched general population. *Appendix Figure 3.1* shows the five-year survival curves after diagnosis of the first AIDS-defining condition, compared to survival for all people with HIV as well as survival after diagnosis of several common, non-AIDS-defining comorbidities.

Observed underlying causes of death are presented in *Appendix Table 3.1*. Although the AIDS-related death rate has decreased significantly since the advent of cART, the continued occurrence of deaths due to AIDS is driven largely by the persistent high proportion of newly diagnosed HIV-positive individuals who present late for care with advanced immune deficiency. As such, the rate still falls short of the aim of zero AIDS-deaths by 2022, as stated in the Netherlands' National Action Plan on STIs, HIV and Sexual Health[25]. *Table 3.1* shows the characteristics of adults living with HIV who died of AIDS, compared to those who died of non-AIDS causes in the period 2010-20. Individuals who died of AIDS were more frequently female, non-MSM and/or migrants, more recently diagnosed with HIV, had been on cART for a shorter period of time, and had much lower CD4 counts at diagnosis, with 64.3% qualifying as a very late presenter (CD4 count below 200 cells/mm^3). In addition, these individuals had much lower nadir CD4 counts. In 56% of cases, they did not have controlled viremia, and 9.2% of this group was not using any ART at the time of death, either because ART had not been started or had been discontinued (*Table 3.1*). Among individuals who died of AIDS but did not classify as (very) late presenters (i.e., they had a CD4 count above 350 cells/mm^3 at diagnosis), the cause of death was relatively more likely to be an AIDS-related haematological malignancy, which are also known to occur in people on suppressive ART with high CD4 counts. The proportion and absolute number of deaths due to non-AIDS-defining conditions have increased significantly over time (*Figure 3.2*), primarily as a consequence of the ever increasing size and average age of the population of people with HIV in the Netherlands. People with HIV that were born in the Netherlands, MSM and men in general are overrepresented among those who died of non-AIDS causes, because people in these three (overlapping) categories have a higher average age compared to migrants, HIV transmission categories other than MSM, and women. Independent risk factors for death and for being diagnosed with an AIDS-defining condition are listed in *Appendix Table 3.2*.

Table 3.1: *Characteristics of adults with HIV who died of AIDS compared to adults with HIV who died of non-AIDS causes in the period 2010-2020.*

	Died of non-AIDS causes	Died of AIDS	p-value
Number of subjects	1,458 (83.2%)	294 (16.8%)	
Age	58.1 (50.4-66.6)	52.6 (44-60.4)	<.001
Male sex	1,278 (87.7%)	236 (80.3%)	0.001
Dutch origin	1,030 (70.6%)	178 (60.5%)	<.001
Men who have sex with men	820 (56.2%)	125 (42.5%)	<.001
Heterosexual men and women	364 (25.0%)	102 (34.7%)	<.001
Other transmission categories	274 (18.8%)	67 (22.8%)	0.125
Years since HIV diagnosis	13.8 (7.32-20.5)	5.93 (0.69-13.6)	<.001
Years since start of cART	11.4 (5.31-16.8)	2.05 (0.34-11.4)	<.001
CD4 at HIV diagnosis	280 (100-500)	109 (30-308)	<.001
Late presenter (CD4 <350 at entry in care)	831 (57.1%)	227 (78.8%)	<.001
Very late presenter (CD4 <200 at entry)	550 (37.7%)	189 (64.3%)	<.001
CD4 nadir	130 (50-240)	44 (10-100)	<.001
Last CD4 measured before death	460 (270-660)	110 (38-270)	<.001
Not undetectable at moment of death	248 (17.2%)	156 (56.3%)	<.001
Not on cART at moment of death	71 (4.9%)	27 (9.2%)	0.005

Legend: *cART=combination antiretroviral therapy. Data shown are n (%) for categorical variables and median (interquartile ranges) for continuous variables. CD4 counts are expressed as cells/mm³.*

Figure 3.1: *(A) Annual mortality and (B) incidence of AIDS in 28,240 HIV-1-positive individuals in the Netherlands after entry into HIV care from 1996 onwards. Solid lines represent the incidence, while the shaded areas are the 95% confidence intervals. The dashed line is the mortality rate for age-matched and sex-matched individuals from the general population in the Netherlands.*

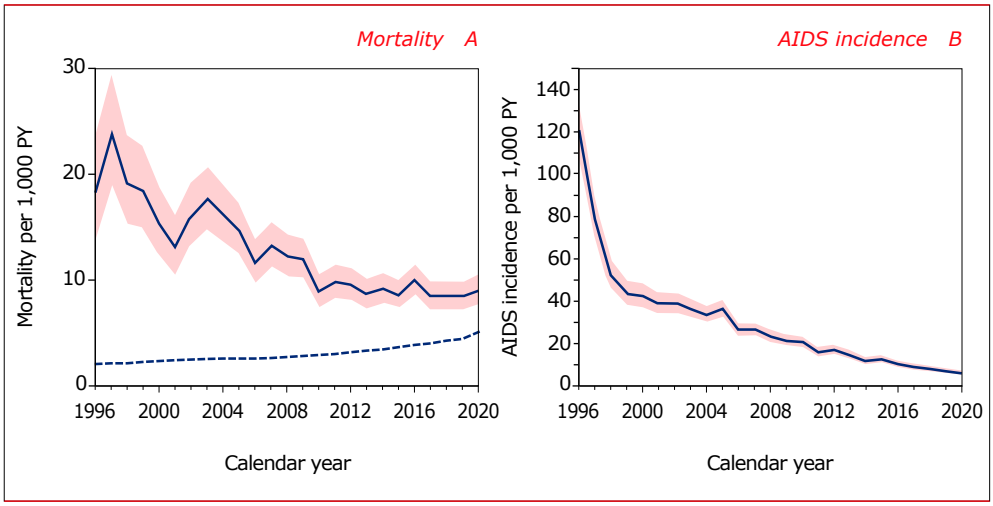
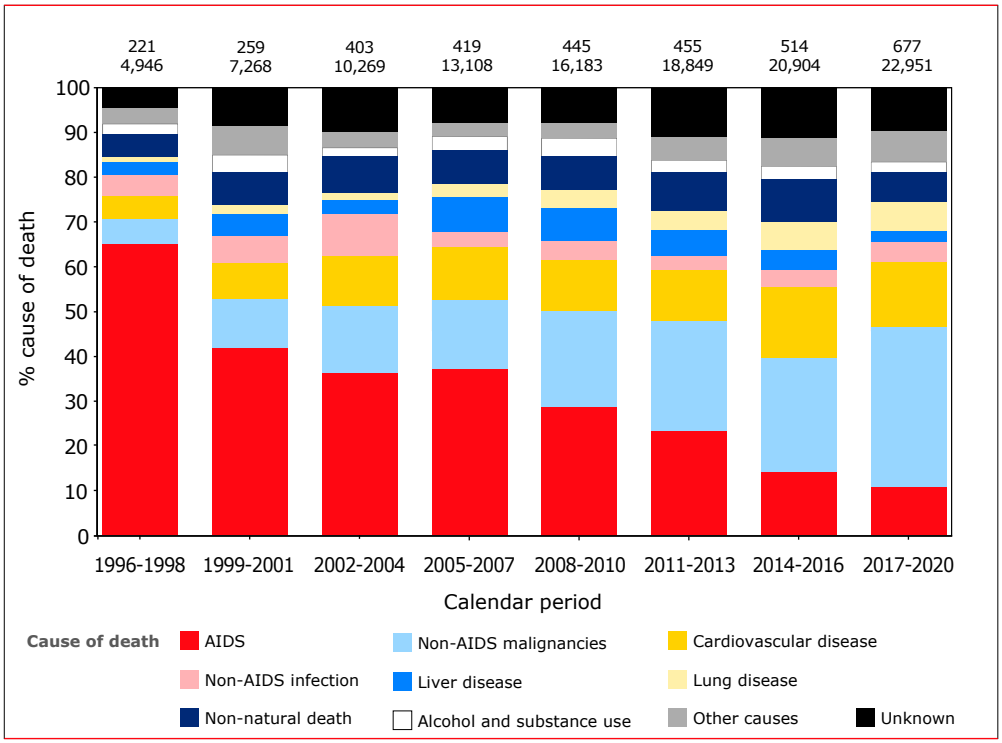


Figure 3.2: Relative changes in causes of death in different calendar periods since the introduction of combination antiretroviral therapy (cART) in the Netherlands. The numbers at the top of each bar represent the total number of deaths and the total number of individuals that were at risk during that calendar period. Mortality attributed to 'alcohol use' refers to deaths due to complications of alcohol-related liver cirrhosis.



We used Poisson regression analysis to examine factors associated with mortality in individuals from the moment they started cART. After correction for all variables listed in *Appendix Table 3.2*, including time-updated age and time-updated lagged CD4 cell counts, we found that, in general, risk of death was higher in men compared to women, and this risk increased as individuals grew older. It also increased if they belonged to the HIV transmission risk group of people who use/used injecting drugs (PWUID); had a prior AIDS diagnosis; were co-infected with the hepatitis B virus (HBV) or hepatitis C virus (HCV); were underweight; were current or past smokers; had spent more time with an HIV RNA level above 1,000 copies/ml while on cART; or had a current CD4 cell count less than 500 cells/mm^3, with the risk of death progressively increasing in lower CD4 strata.

Although a lower mortality risk was observed in individuals of non-Dutch origin, this is likely due to a larger proportion of people from sub-Saharan Africa, and other individuals not born in the Netherlands (with the exception of those born in Surinam or the Dutch Antilles), being lost to follow up (*Appendix Table 3.3*). In native Dutch individuals, and those from Surinam and the Dutch Antilles, the risk of becoming lost to follow up was not linked to their CD4 count. In contrast, people from all other non-Dutch groups were far more likely to become lost to follow up if they had very low CD4 counts. One explanation could be that those born overseas often return to their families in their country of origin when they experience a severe deterioration in health. As a result, it is likely that mortality rates in these groups have been considerably underestimated.

Individuals who had a psychiatric disease as the recorded underlying cause of death, and for whom the immediate cause of death was recorded as suicide, have been re-classified as 'suicide' for the current analysis (*Appendix Table 3.1*). The number of recorded suicides among people living with HIV in the Netherlands in the period 2011 to 2020 was stable at around ten recorded cases per calendar year, which is much higher than the known rates of suicide in the general Dutch population (which has 10.5 instances per 100,000 individuals per year compared to more than 40 in the population living with HIV)[26]. For patients with a serious somatic condition, who opted for euthanasia in the terminal disease stage, the underlying somatic condition was recorded as the cause of death. In the entire follow-up period from 1996 to 2020, a total of 138 instances of euthanasia were recorded; 33% of cases occurred in patients who died of AIDS, 41% in patients who died of non-AIDS-defining malignancies, and the remaining 26% in patients who died of other diseases. Our definition of euthanasia does not include the use of standard practice palliative care, like palliative sedation in the terminal phase of the underlying disease.

AIDS-defining events

In the group of 28,240 HIV-1-positive adults ever registered in the SHM database, the incidence of AIDS decreased sharply from 121.0 (95% CI 108.4-134.5) in 1996 to 6.2 (95% CI 5.1-7.5) cases per 1,000 PYFU in 2020 (*Figure 3.1B*). *Appendix Table 3.4* gives an overview of the AIDS events occurring between 1996 and 2020. The most common AIDS events between 2016 and 2020 were *Pneumocystis jirovecii* pneumonia (21% of all events); oesophageal candidiasis (17%); Kaposi's sarcoma (11%); tuberculosis (pulmonary 8%, extrapulmonary 5%); lymphoma (6%); recurrent bacterial pneumonia (5%); AIDS-related wasting (5%); toxoplasmosis of the brain (4%); AIDS dementia complex/HIV encephalopathy (3%); and cytomegalovirus-associated end organ disease (3%). Risk factors for AIDS-defining events are shown in *Appendix Table 3.2*.

In the present analyses, we concentrate on the first occurrence of any AIDS-defining event after the start of cART. The results of these analyses show that individuals were more likely to experience their first AIDS-defining event if they were older, had a current CD4 cell count below 500 cells/mm^3 (although the likelihood was even higher if their CD4 cell count was below 200 or 50 cells/mm^3), had more than 1,000 HIV RNA copies/ml for a longer period of time while on cART, or were co-infected with HCV.

Because the main findings of the analysis of AIDS events after the start of cART were heavily influenced by events occurring shortly after the start of cART and/or while HIV-1 RNA was still detectable, we also analysed the incidence of CDC-B and AIDS-defining events in individuals who had started cART at least one year before and had undetectable viraemia or transient low-level viraemia (i.e., 'blips', below 200 copies/ml), at the moment the HIV-related event was diagnosed: in other words, we focused on those individuals with an optimal response to cART. Events were classified into CD4 strata based on the current or previously measured CD4 count, whichever was the lowest. Use of opportunistic infection prophylaxis was not accounted for in this analysis. Only 'definitive' or 'probable' diagnoses were considered; 'possible' events or events with incomplete ascertainment were excluded. Between 1 January 2000 and 31 December 2020, 24,863 individuals contributed a total of 221.8 thousand PYFU, during which 3,423 CDC-B and/or AIDS-defining events were diagnosed. This resulted in an incidence rate of 15.4 events per 1,000 PYFU (2,110 CDC-B events, 9.5 events/1,000 PYFU; 1,313 CDC-C/AIDS events, 5.9 events/1,000 PYFU) (*Table 3.2*). As expected, the incidence rates were highest in the CD4 strata below 200 cells/mm^3. Although the incidence rates declined sharply in the higher CD4 strata, the incidence rates in the 200-349 and 350-499 cells/mm^3 strata remained substantial, with 10.6 and 5.8 AIDS-defining illnesses/1,000 PYFU, respectively. The incidence rates of AIDS-defining illnesses in the CD4 strata of 500-749 and over 750 cells/mm^3 were 3.0 (95% CI 2.6-3.4) and 1.9 (95% CI 1.6-2.3) events/1,000 PYFU, respectively. Note that the incidence in the over 750 cells/mm^3 stratum is statistically significantly lower than in the 500-749 cells/mm^3 stratum. In these highest CD4 strata, the main AIDS-defining events that still occurred were recurrent bacterial pneumonia, Kaposi's sarcoma, oesophageal candidiasis, non-Hodgkin's lymphoma, tuberculosis (pulmonary and extrapulmonary), chronic genital Herpes simplex virus (HSV) ulcers, and AIDS dementia complex (*Appendix Table 3.6* shows the type and number of HIV-related diagnoses by CD4 strata).

Table 3.2: CDC-B and CDC-C/AIDS events occurring between 2000 and 2020 in individuals on cART, while having an undetectable viral load.

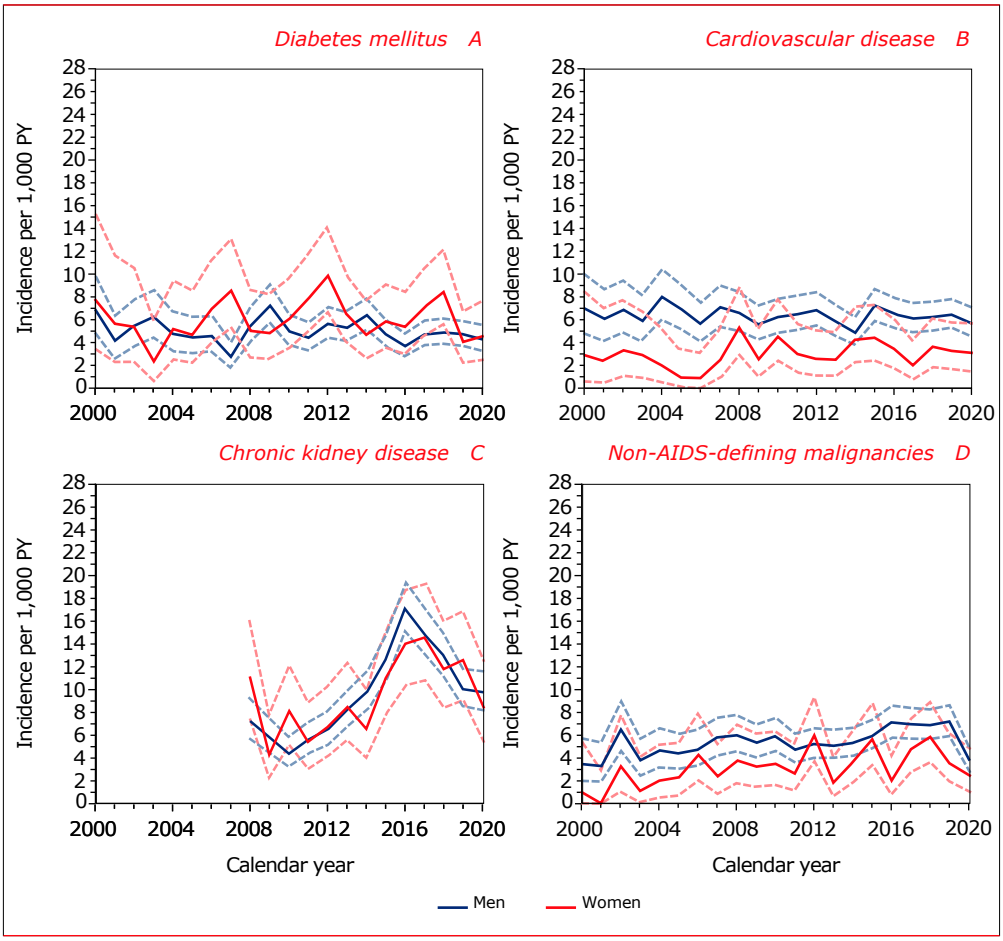
CD4 category (cells/mm³)	CDC events (n)	CDC B events (n)	CDC C events (n)	PYFU follow-up (x1000)	Incidence rate CDC events (/1000 PY) (95%CI)	Incidence rate CDC-B events (/1000 PY) (95%CI)	Incidence rate CDC-C events (/1000 PY) (95%CI)
0-49	224	93	131	0.5	481 (420-549)	200 (161-245)	282 (235-334)
50-199	636	348	288	8.0	79.2 (73.1-85.6)	43.3 (38.9-48.1)	35.8 (31.8-40.2)
200-349	719	442	277	26.1	27.5 (25.6-29.6)	16.9 (15.4-18.6)	10.6 (9.39-11.9)
350-499	659	397	262	45.5	14.5 (13.4-15.6)	8.73 (7.89-9.63)	5.76 (5.09-6.50)
500-749	738	504	234	78.4	9.41 (8.74-10.1)	6.43 (5.88-7.01)	2.98 (2.61-3.39)
750+	447	326	121	63.3	7.07 (6.43-7.75)	5.15 (4.61-5.75)	1.91 (1.59-2.29)
Total	**3423**	**2110**	**1313**	**221.8**	**15.4 (14.9-16.0)**	**9.51 (9.11-9.93)**	**5.92 (5.60-6.25)**

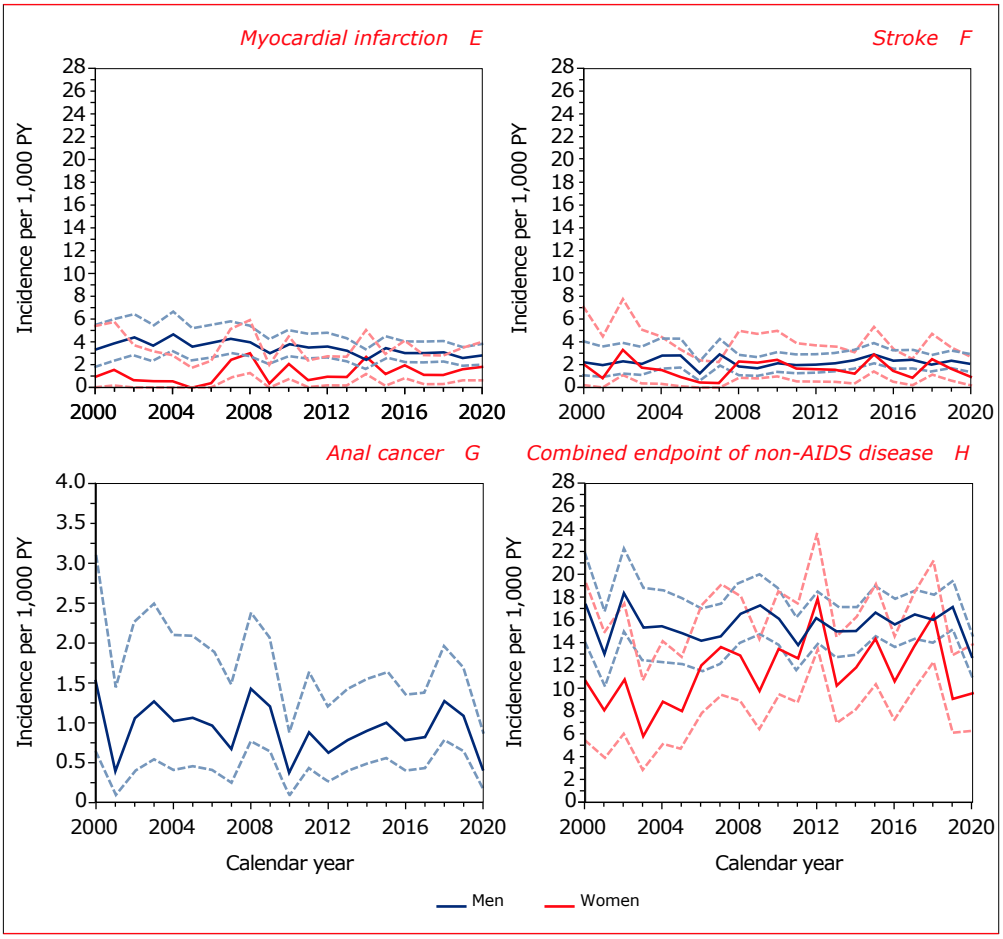
***Legend:** CDC=Centers for Disease Control and Prevention Classification System for HIV Infection; CDC-B=moderately symptomatic HIV disease; CDC-C=AIDS-defining events; cART=combination antiretroviral therapy; PYFU=person years of follow up.*

Non-AIDS-defining events

Of the 28,240 HIV-1-positive adults ever registered with SHM, 27,896 were aged 18 years or older while in follow up in, or after January 2000. For these treated and untreated adults, we report incidence figures and risk factors for diabetes mellitus; a composite cardiovascular disease endpoint (separately for myocardial infarction and stroke); non-AIDS-defining malignancies (both overall and separately for anal cancer); and CKD. We also present the incidence of the first occurrence of diabetes mellitus, cardiovascular disease, or non-AIDS-defining malignancies as a combined non-AIDS disease endpoint (*Figure 3.3*).

Figure 3.3: *Crude incidence rates per 1,000 person years of follow up (solid lines) and 95% confidence intervals (dotted lines) of (A) diabetes mellitus, (B) cardiovascular disease, (C) chronic kidney disease, (D) non-AIDS-defining malignancies, (E) myocardial infarction, (F) stroke, (G) anal cancer, and (H) combined endpoint of non-AIDS disease (diabetes mellitus, cardiovascular disease, and non-AIDS-defining malignancies), by gender, with the exception of anal cancer, which is presented for males only.*





Diabetes mellitus

Of the 27,896 individuals aged 18 years or older and in follow up in, or after January 2000, a total of 1,476 (1,140 men and 336 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.3A*) and, in 2020, was 4.3 (95% CI 3.3-5.5) per 1,000 PYFU in men and 4.6 (95% CI 2.5-7.6) per 1,000 PYFU in women. In men, the age-standardised incidence ratio declined over time and was significantly lower in 2016-20 than in 2000-10 and 2011-15. Whereas, in women, the age standardised incidence in 2000-10 and 2011-15 was not significantly different from that in 2016-20 (*Table 3.3*).

Demographic and clinical factors independently associated with an increased risk of new-onset diabetes mellitus were: male gender; non-Dutch origin (in particular people born in sub-Saharan Africa, South Asia, and the Caribbean); older age group; acquiring HIV heterosexually or through injecting drug use; a BMI greater than 25 kg/m^2 or below 18 kg/m^2; hypertension; a latest CD4 cell count below 200 cells/mm^3; pre-treatment with nucleoside analogue reverse transcriptase inhibitors (NRTIs) prior to starting cART; and a prior AIDS diagnosis (*Appendix Table 3.5*). Moreover, the risk of new-onset diabetes in the periods 2000-10 and 2011-15 was significantly higher than in the period 2016-20. A longer time on didanosine was also significantly associated with an increased risk.

Table 3.3: *Crude incidence of diabetes mellitus per 1,000 person years of follow up in 2000–2010, 2011–2015 and 2016–2020 and age-standardised incidence ratio (indirect method) with 95% confidence intervals.*

Calendar year	Men		Women	
	Incidence/1000 PYFU (95%CI)	Standardised incidence ratio* (95% CI)	Incidence/1000 PYFU (95%CI)	Standardised incidence ratio* (95% CI)
2000–2010	5.2 (4.7–5.7)	1.51 (1.36–1.65)	5.7 (4.8–6.8)	1.04 (0.86–1.22)
2011–2015	5.3 (4.8–5.9)	1.32 (1.18–1.46)	6.9 (5.6–8.3)	1.20 (0.97–1.43)
2016–2020	4.5 (4.1–5.0)	1 (reference)	6.0 (4.9–7.3)	1 (reference)

** Standardised according to the observed age distribution between 2016–2020.*

Legend: *CI=confidence intervals; PY=person years.*

Cardiovascular disease

From January 2000 onwards, 1,613 individuals (1,441 men and 172 women) had a fatal or non-fatal cardiovascular event. Of these, 816 had a myocardial infarction, 572 a stroke, 119 a coronary artery bypass graft, 584 a coronary angioplasty or stenting, and 13 a carotid endarterectomy. The crude incidence over time remained stable and was lower in women than in men (*Figure 3.3B*). The standardised incidence ratio in men and women declined over time (*Table 3.4*).

In the analysis of risk factors, those associated with cardiovascular disease were: male gender; Dutch origin; older age group; acquiring HIV through MSM contacts or through injecting drug use; a latest CD4 cell count below 350 cells/mm^3; a prior AIDS diagnosis; pre-treatment with NRTIs before starting cART; use of abacavir (either currently or in the last six months); current and past smoking; and presence of hypertension. Estimated cardiovascular risk using the D:A:D algorithm was also higher during 2000-10 and 2011-15 than during 2016-20, independent of other variables included in the analysis (*Appendix Table 3.5*). The strong positive association between use of abacavir and CVD was independent of renal function.

When eGFR estimated using the Cockcroft-Gault method (available from 2007 onwards) was included in the model, the abacavir effect was only slightly attenuated, decreasing from an incidence risk ratio (IRR) of 1.58 to 1.45, p<0.001. Compared to having an eGFR above 90 ml/min, having an eGFR below 60 ml/min was independently associated with a higher risk of CVD; at 60-90 ml/min, the IRR was 1.09 (95% CI 0.95-1.24), p=0.22; at 30-60 ml/min the IRR was 1.72 (1.41-2.10), p<0.001; at 15-30 ml/min, the IRR was 4.56 (3.08-6.73), p<0.001; and at 0-15 ml/min the IRR was 3.59 (2.01-6.42), p<0.001.

From January 2000 onwards, 207 men and 20 women experienced a fatal or non-fatal secondary cardiovascular event (129 had a myocardial infarction, 107 had a stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2020 in men and women with a prior cardiovascular event was 27.4 (95% CI 23.8-31.4) and 19.7 (95% CI 12.0-30.4), respectively. The crude rate and age-standardised incidence ratio (SIR; indirect method) of secondary myocardial infarction and stroke per 1,000 PYFU changed significantly during 2000-10 (crude rate: 30.9 events per 1,000 PYFU; SIR: 1.25, 95% CI 0.97-1.52), but not during 2011-15 (crude rate: 24.4 events per 1,000 PYFU; SIR: 0.98, 95% CI 0.73-1.22) compared with the reference period 2016-20 (crude rate: 24.9 events per 1,000 PYFU).

Table 3.4: *Crude incidence of cardiovascular disease per 1,000 person years of follow up in 2000–2010, 2011–2015, and 2016–2020 and age-standardised incidence ratio with 95% confidence intervals.*

Calendar year	Men		Women	
	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio*(95% CI)	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio*(95% CI)
2000–2010	6.5 (6.0–7.1)	1.56 (1.43–1.69)	2.8 (2.2–3.6)	1.56 (1.18–1.94)
2011–2015	6.3 (5.7–6.9)	1.20 (1.08–1.31)	3.4 (2.5–4.4)	1.33 (0.98–1.69)
2016–2020	6.2 (5.7–6.8)	1 (reference)	3.1 (2.3–4.0)	1 (reference)

** Standardised according to the observed age distribution in 2016–2020.*

Legend: *CI=confidence intervals; PY=person years.*

Trends in cardiovascular risk factors

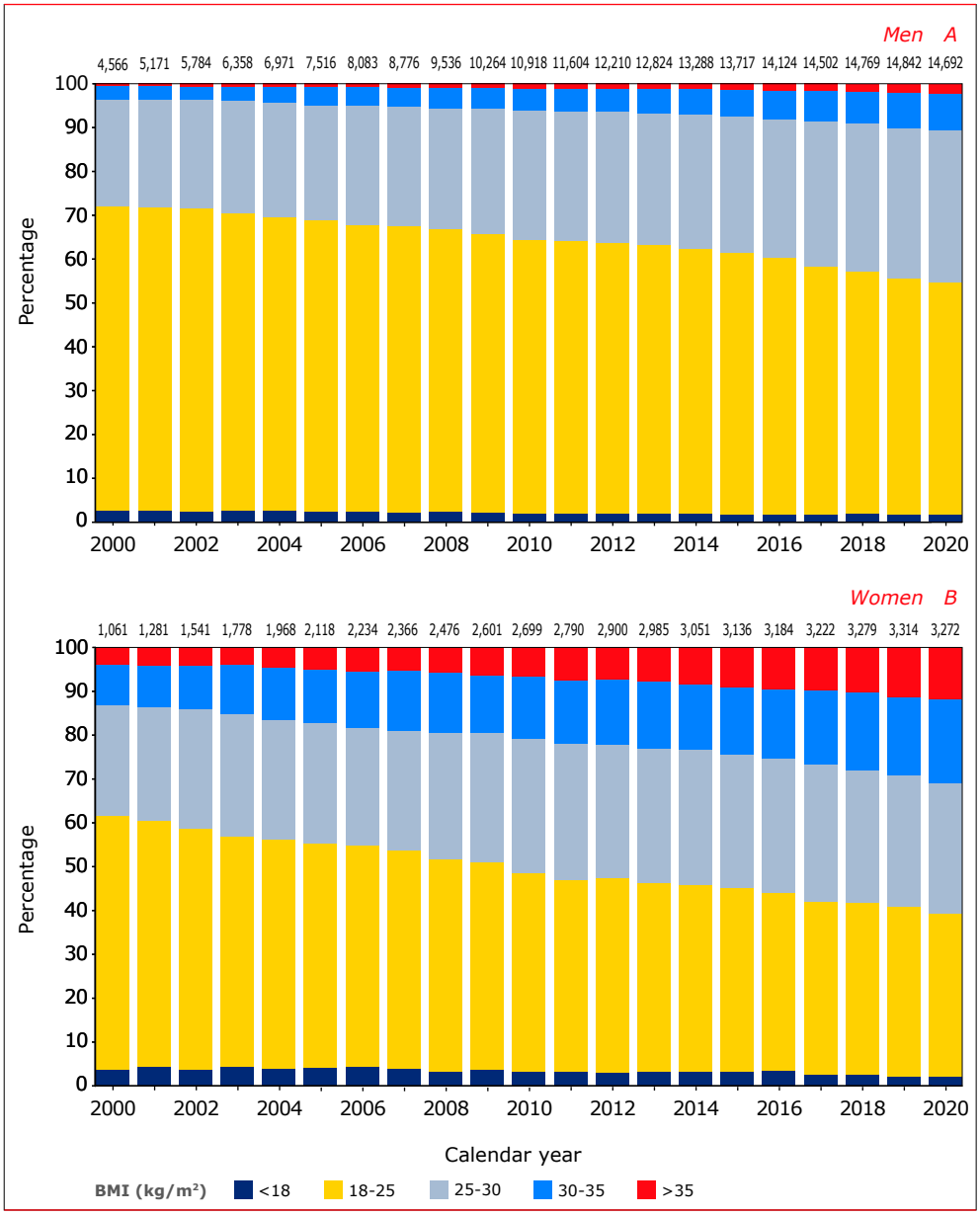
Figures 3.4A and *3.4B* show that the distribution of body mass index (BMI) of both men and women in the HIV-1-positive population has increased over time. In 2020, the proportion of men with available BMI data who were overweight (25-30 kg/m^2), or obese (WHO class I: 30-35 kg/m^2 and WHO class II/III: 35 kg/m^2 or over), was 34.6%, 8.5% and 2.2%, respectively. In women, these proportions were 29.9%, 19.3% and 11.7%, respectively.

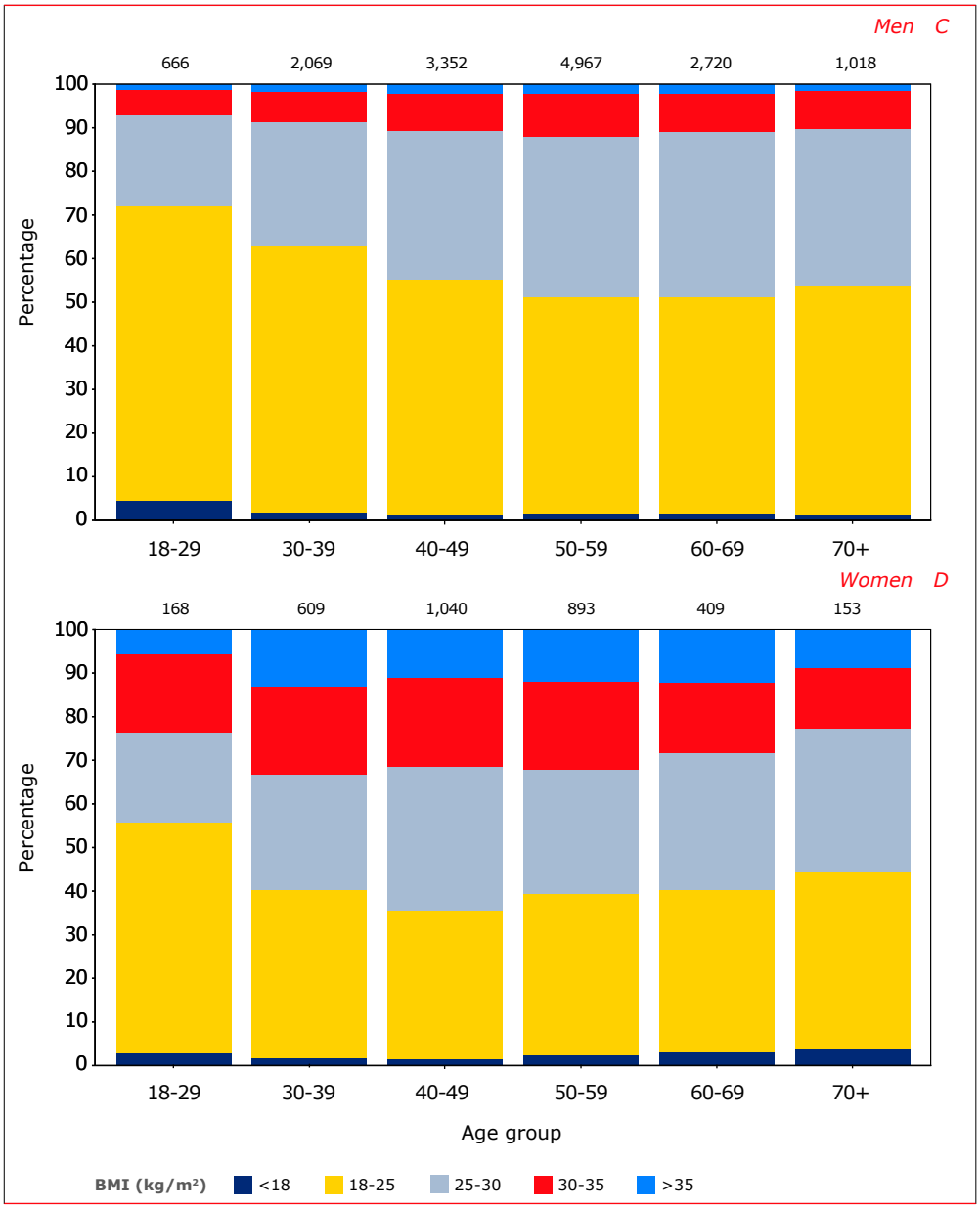
Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the population living with HIV. This analysis revealed that the increase was at least partially driven by changes over time in population demographic characteristics (age, region of origin, HIV transmission category) and time since first start of cART, and that this effect was more marked in men than in women.

With regard to specific antiretroviral agents, the use of bictegravir, dolutegravir, rilpivirine and tenofovir alafenamide were all independently associated with higher body weight. *Figures 3.4C* and *3.4D* show the distribution of BMI according to age groups in 2020 for men and women. Whereas in adult men of all age groups, the proportion classified as obese (10.7%) was somewhat lower than the proportion found in the general Dutch male population (12.3%), in women of all age groups there was more obesity (30.0%) than in the general Dutch female population (15.4%)[27]. There were substantial differences between native Dutch people, Western migrants and non-Western migrants: among males, 9.6% of Dutch men, 11.5% of Western migrants and 13.6% of non-Western migrants were obese, whereas in females, those figures were 21.5%, 20.1%, and 37.3%, respectively. Being obese (a BMI over 30) was independently associated with an increased risk of diabetes (IRR 5.13, 95% CI 4.38-6.00, p<0.001), but that was not the case with CVD, CKD or non-AIDS-defining malignancies (*Appendix Table 3.5*).

Figure 3.5A shows that, in 2020, 48.9% of those treated with antihypertensives still had grade 1 hypertension or higher. In 2020, 25.0% (4,031) of individuals not using antihypertensives had grade 1-3 hypertension (*Figure 3.5B*). For 3,745 (92.9%) of these individuals, a five-year cardiovascular disease (CVD) risk could be calculated with the recalibrated D:A:D study algorithm[28]: 219 (5.9%) had a five-year CVD risk of 10% or more; according to the European AIDS Clinical Society (EACS) guidelines, these individuals, in particular, should receive antihypertensive treatment[29]. *Figure 3.6* gives an overview of the cART-treated population's estimated risk of CVD over time. In 2000, the percentage of individuals at high (5-10%) or very high (10% or more) five-year risk were 11.7% and 5.6%, respectively, which steadily increased to 20.4% and 12.1%, respectively, in 2020. The increase in the percentage of individuals at high or very high risk likely reflects the ageing of the population being studied.

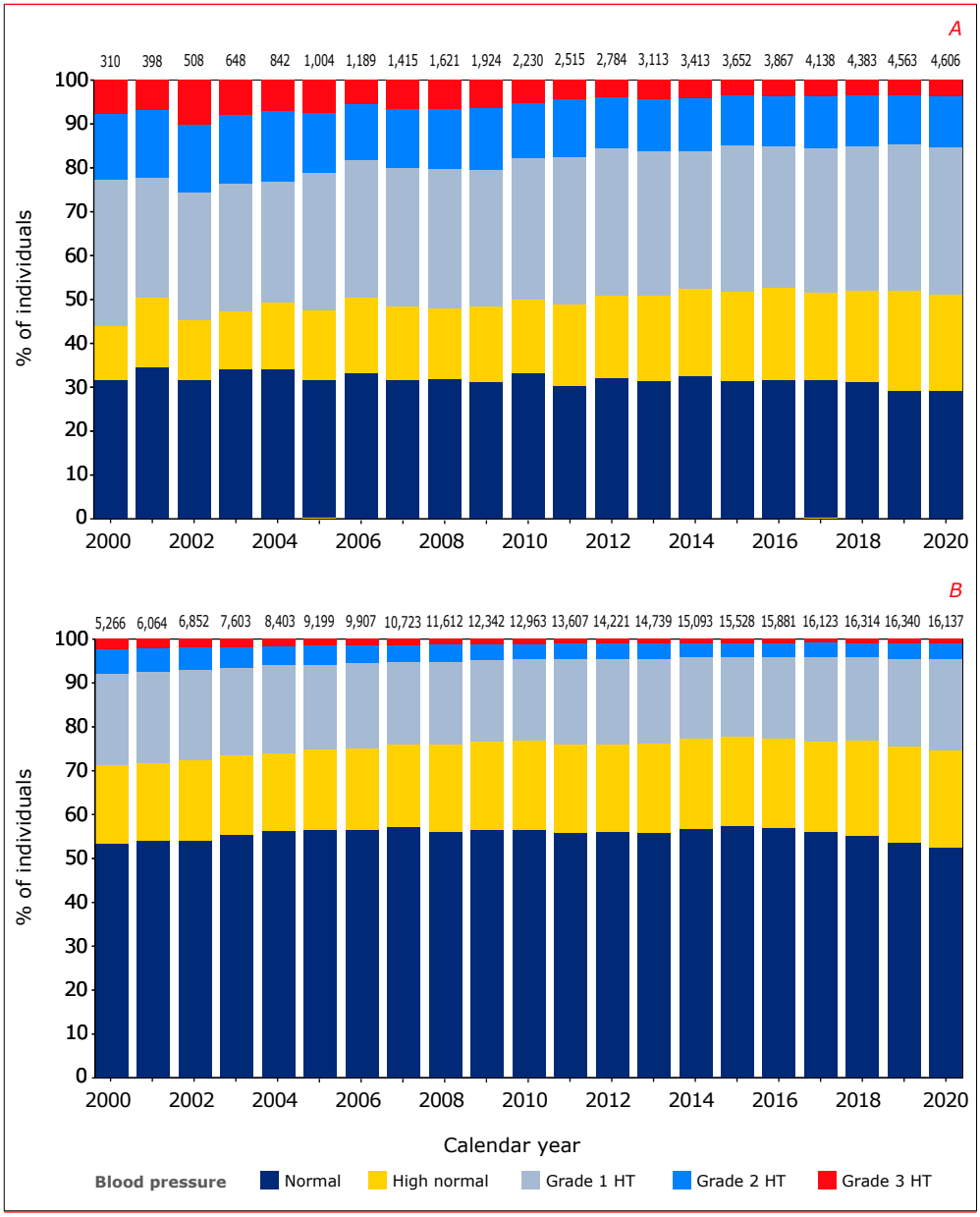
Figure 3.4: Distribution of the body mass index (BMI) at the end of each calendar year in (A) men, and (B) women, as a percentage of the total number of men and women with a known BMI in each year, and distribution of the BMI over the age groups for (C) men, and (D) women, in 2020. For each individual, the last available weight measurement in each year was selected. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year (A & B) or from that age group (C & D).





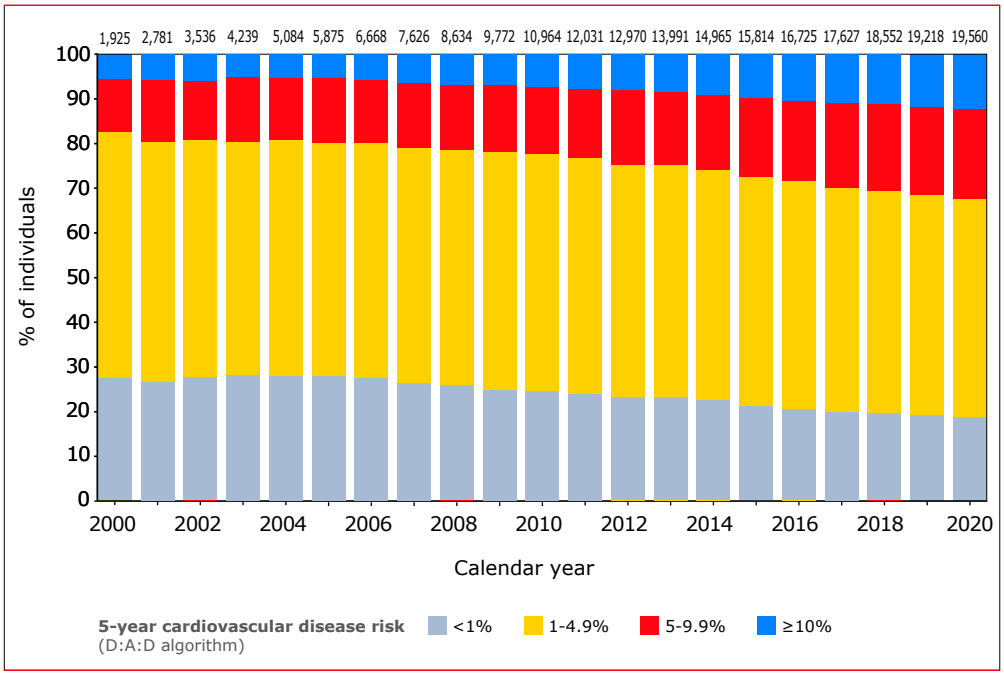
Legend: BMI=body mass index.

Figure 3.5: Distribution of graded blood pressure at the end of each calendar year in (A) individuals known to be receiving antihypertensive treatment, and (B) those individuals not recorded as being treated for hypertension. For each individual, the last available systolic and diastolic blood pressure measurement in each year was selected. Blood pressure was graded according to the classification recommended in the guidelines for the management of arterial hypertension by the European Society of Hypertension and by the European Society of Cardiology[30]. Normal: systolic blood pressure (SBP) <130 mmHg or diastolic blood pressure (DBP) <85 mmHg; high normal: SBP 130–139 mmHg or DBP 85–89 mmHg; grade 1 hypertension SBP 140–159 mmHg or DBP 90–99 mmHg; grade 2 hypertension SBP 160–179 mmHg or DBP 100–109 mmHg; grade 3 hypertension SBP ≥ 180 mmHg or DBP ≥ 110 mmHg. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.



Legend: BP=blood pressure; HT=hypertension.

Figure 3.6: Estimated five-year risk of coronary heart disease at the end of each calendar year according to the algorithm from the D:A:D: study[28]. Calculation of risk included variables such as total cholesterol, HDL cholesterol, and systolic blood pressure. Values for these variables were estimated on the basis of a 'last observation carried forward' approach. An accurate assessment of an individual's risk requires recent measurements of lipid levels and blood pressure. Recent HDL cholesterol measurements were often lacking or absent. Risk could not be estimated in younger individuals, in particular, because of missing data. Hence, the reported absolute number of individuals is smaller than the number of individuals in active follow up at the end of each calendar year, and older individuals are over-represented. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.



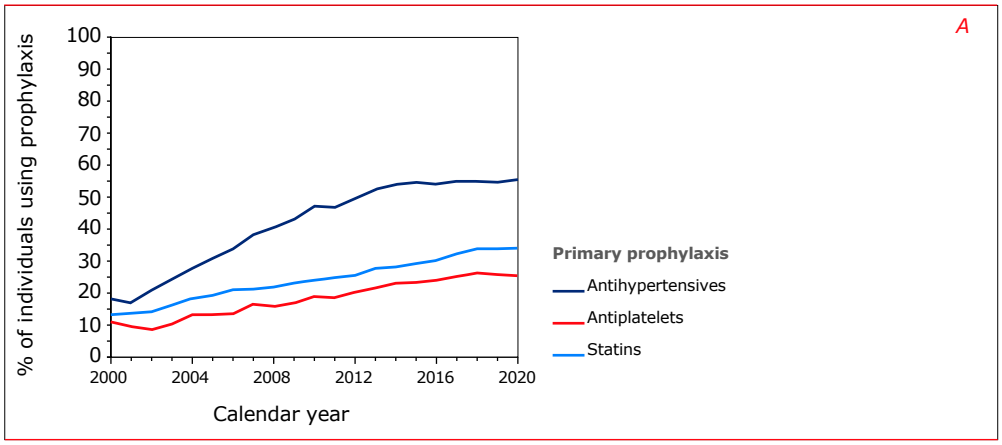
Use of primary or secondary preventive therapy for myocardial infarction or stroke

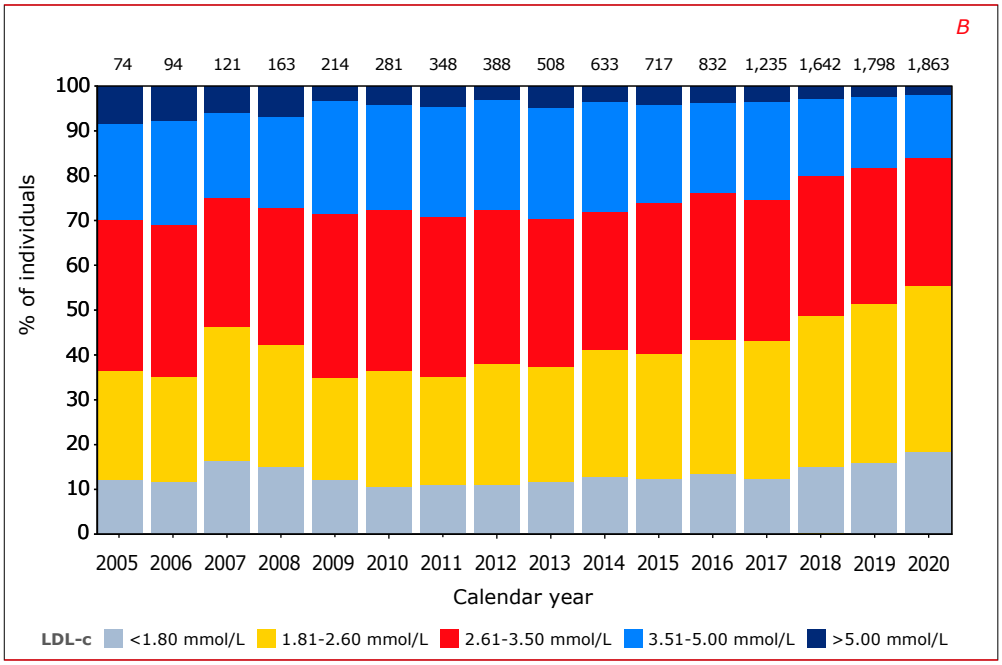
Primary prevention

According to EACS guidelines, statin therapy should be offered to individuals with type 2 diabetes or a ten-year CVD risk same or ≥10%. They also recommend that angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers (CCB), diuretics, and non-dihyropyridine CCB (verapamil or diltiazem) should be offered to individuals with a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and a ten-year CVD risk ≥20%. For individuals aged 50 years or more with a ten-year CVD risk ≥20%, acetylsalicylic acid is recommended[31]. In general, the Dutch cardiovascular risk management (CVRM) guidelines closely resemble the EACS guidelines, with the notable exception that the Dutch guidelines do not recommend the use of

acetylsalicylic acid in older people with increased CVD risk, but without prior clinical CVD[32]. *Figure 3.7A* shows trends in the use of these medications in individuals without a prior stroke, myocardial infarction, or cardiovascular surgical procedure. The percentage of individuals for whom primary prevention with statins and the above-mentioned antihypertensive agents (referred to collectively hereafter as antihypertensives) is recommended, has increased over time, although the curve for antihypertensives has levelled off somewhat since 2013. Although the percentage of individuals who were at high risk, aged 50 years or older, and used acetylsalicylic acid/clopidogrel as primary prevention, increased slowly prior to 2014, the overall proportion remained minimal and has remained stable during the last years. Only about half the individuals who received treatment with antihypertensive agents or statins for the primary prophylaxis of myocardial infarction or stroke reached treatment targets (below 2.6 mmol/l). *Figure 3.5A* shows that of all individuals using antihypertensive agents, only about half had a normal blood pressure in recent years. *Figure 3.7B* shows the distribution of LDL-cholesterol in subjects who use statins for primary CVD prophylaxis. The proportion of individuals with an LDL-c below 1.8 mmol/l or between 1.8 and 2.6 mmol/l was 12.2% and 24.3%, respectively, in 2005, and increased to 18.7% and 36.7%, respectively, in 2020.

Figure 3.7: *(A) Percentage of individuals without a previous myocardial infarction, stroke, or cardiovascular surgical procedure who, according to European AIDS Clinical Society (EACS) guidelines, should be offered statin therapy, antiplatelet therapy, or antihypertensives for primary prevention of myocardial infarction or stroke. (B) Distribution of LDL-cholesterol in individuals using statins for primary prevention of myocardial infarction or stroke.*

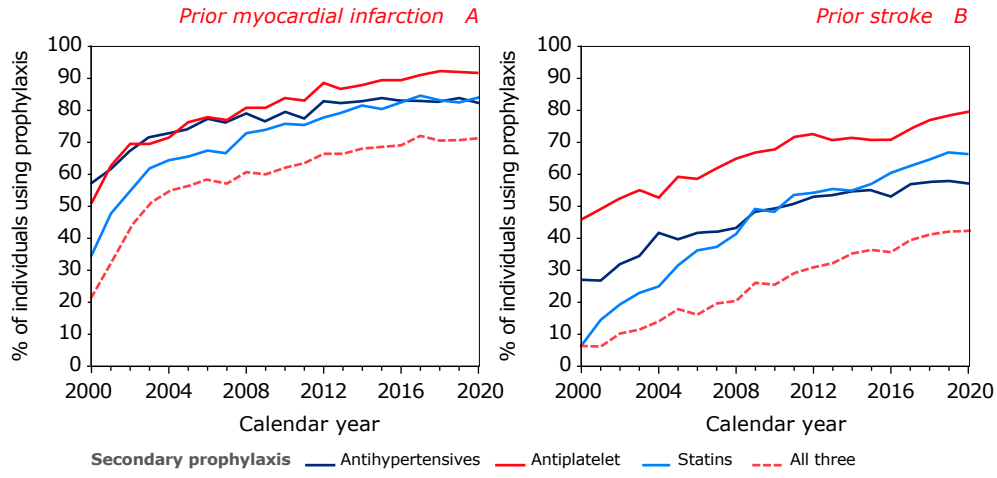




Secondary prophylaxis for myocardial infarction or stroke

According to all guidelines, individuals with a prior myocardial infarction or ischaemic stroke should receive lifelong treatment with statins, antihypertensives (ACE inhibitors, beta blockers or angiotensin receptor blockers), as well as low-dose acetylsalicylic acid/clopidogrel[33,34]. *Figure 3.8A* shows that the percentages of individuals using statins, acetylsalicylic acid/clopidogrel, or antihypertensives after a myocardial infarction increased between 2000 and 2020: in 2020, 84.0% of individuals with a prior myocardial infarction used statins, 82.5% used antihypertensives, and 91.8% used acetylsalicylic acid/clopidogrel. Although the use of statins and antihypertensives after an ischaemic stroke also increased over time, in 2020 these medications were used less frequently after a stroke than after a myocardial infarction (66.5% used statins, 57.4% used antihypertensives, and 79.7% used acetylsalicylic acid/clopidogrel) (*Figure 3.8B*).

Figure 3.8: Percentage of individuals with (A) myocardial infarction or (B) ischaemic stroke using statin therapy, antiplatelet therapy, or antihypertensives.



Chronic kidney disease

Glomerular filtration rate (GFR) is a marker of renal function and is commonly estimated by one of three formulae, namely, the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations[35]. As all three equations used to estimate GFR (eGFR) are based on serum creatinine, they may be markedly affected by rapid changes in muscle mass, as is seen in some individuals with advanced HIV disease who commence cART. Of these equations, both the Cockcroft-Gault and the CKD-EPI equations have been validated in individuals living with HIV[35,36]. However, because the CKD-EPI equation is the one most often used in clinical practice, we have chosen to report eGFR values as estimated by this equation. The distribution of eGFR categories in ml/min/1.73m^2 (90 or above, normal kidney function; 60-89, mildly reduced; 30-59, moderately reduced; 15-29, severely reduced; and below 15, very severely reduced kidney function) is shown in *Figures 3.9A* and *3.9B* for men and women. The percentage of men with normal kidney function decreased over time from 74.5% in 2007, to 44.9% in 2020, and this pattern was similar in women. Typically, eGFR decreases with increased age, as shown in *Figure 3.10*, and therefore, the decrease in the proportion of individuals with normal function over time is likely due, in part, to the increasing age of individuals in care.

CKD incidence and risk factors

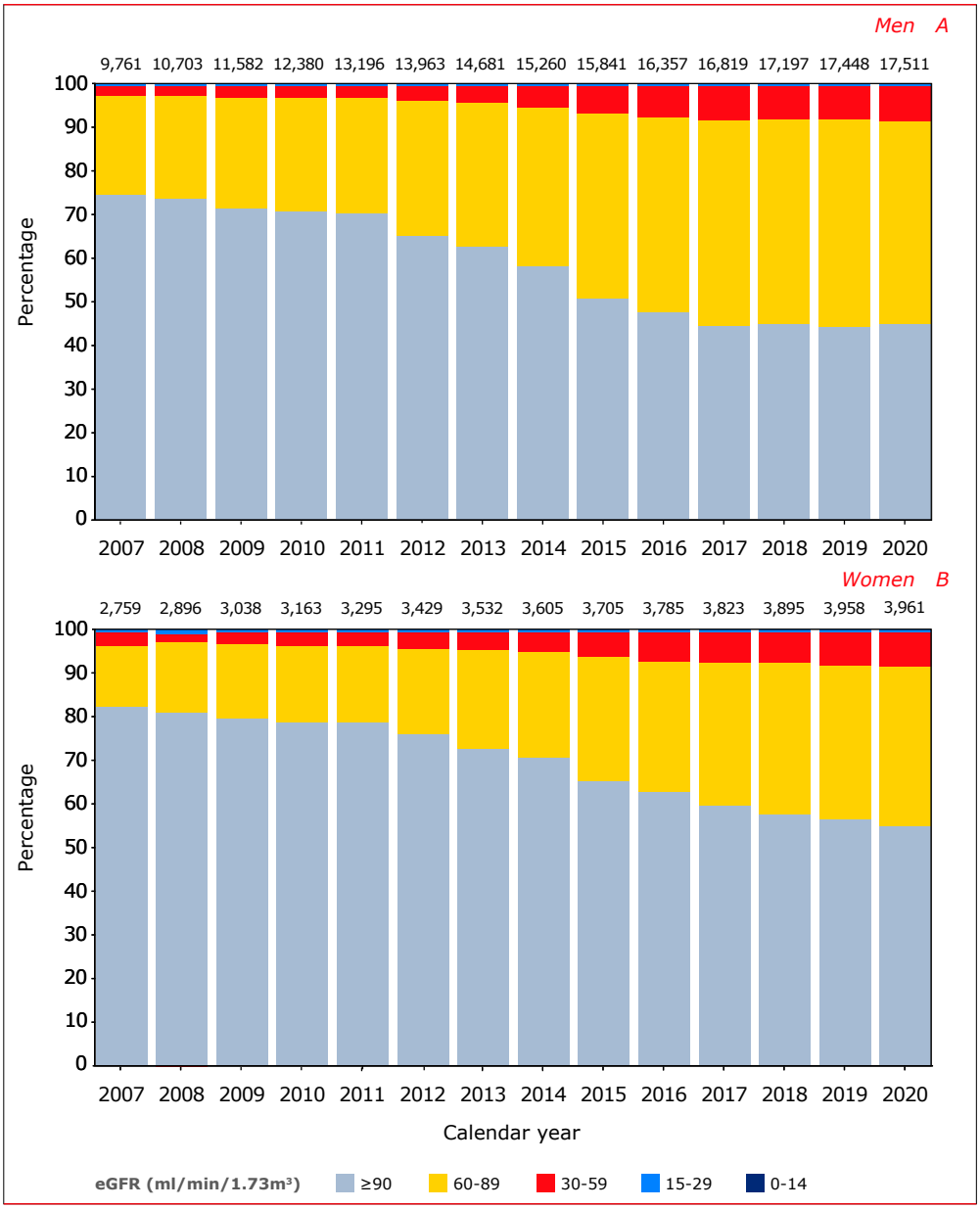
In individuals with an eGFR above 60ml/min/1.73m^2 at the time of inclusion in the analyses, who did not have a previously confirmed CKD, the crude incidence of CKD, defined as eGFR below 60ml/min/1.73m^2 confirmed by a second test at least 26 weeks later, varied over time (*Figure 3.3C*). Routine collection of serum creatinine measurements commenced in 2007. To avoid misclassifying prevalent CKD as incident CKD, we used serum creatinine levels measured in 2007 to distinguish between prevalent (i.e., CKD already present in 2007), versus new-onset incident cases of CKD (i.e., no CKD observed in 2007), from 2008 onwards. In men, the incidence rose from 7.1 cases per 1,000 PYFU in the period 2008-14 to 11.9 in 2015-20. In women, the incidence rose from 7.3 to 12.7 cases per 1,000 PYFU during the same periods (*Table 3.5*). The age-standardised incidence ratio in men and women increased significantly over time (*Table 3.5*).

Risk factors for CKD included: female gender; Dutch origin; low current CD4 cell count (below 200 cells/mm^3); a prior AIDS diagnosis; belonging to the HIV transmission risk group of people who inject drugs; older age group; lower body mass index; hypertension; diabetes mellitus; cardiovascular disease; pre-treatment with monotherapy and dual therapy with nucleoside analogues before the start of cART; and chronic HBV and HCV co-infection (*Appendix Table 3.5*). When current use of cobicistat, rilpivirine, dolutegravir, and bictegravir were added to the model, the increased risk of CKD in the calendar period 2016-20 completely disappeared in comparison to 2008-10 and 2011-15. This strongly suggests that the increase in CKD seen in recent years is largely due to increases in serum creatinine caused by ARV-induced reversible inhibition of two transporters that mediate tubular secretion of creatinine, without affecting the true glomerular filtration rate (namely, organic cation transporter 2 (OCT2), and multidrug and toxin extrusion transporter (MATE1)) and is therefore not a true increase in CKD.

Tenofovir disoproxil fumarate (TDF) can cause true decreases of the GFR. We investigated changes in serum creatinine levels in subjects who switched from a stable (longer than 12 months) TDF-containing regimen to a TAF-containing regimen. We compared the serum creatinine levels measured in the three months prior to the switch, to serum creatinine levels measured at least six months after the switch. This analysis was limited to subjects who did not start or stop OCT2 / MATE1 inhibitors within the 12 months prior to, and six months following, the switch from TDF to TAF. A total of 393 subjects fulfilled the above criteria and switched from TDF to TAF because of renal toxicity / elevated serum creatinine. Another 2,916 subjects also fulfilled the above criteria but switched from TDF to TAF for other reasons. The 393 subjects who switched because of presumed TDF-

associated renal toxicity, had a median serum creatinine level of 115 (IQR 106-125) mmol/l prior to the switch, and showed a median change of -7 (IQR -16 to 0) mmol/l 6 months or longer after the switch. The 2,916 subjects who switched because of other reasons had a median serum creatinine level of 88 (IQR 77-100) mmol/l prior to the switch, and showed a median change of -1 (IQR -7 to +5) mmol/l 6 months or longer after the switch.

Figure 3.9: *Distribution of categories of estimated glomerular filtration rate (eGFR) at the end of each calendar year in (A) men, and (B) women. For each individual, the last available measurement in each year was selected. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.*



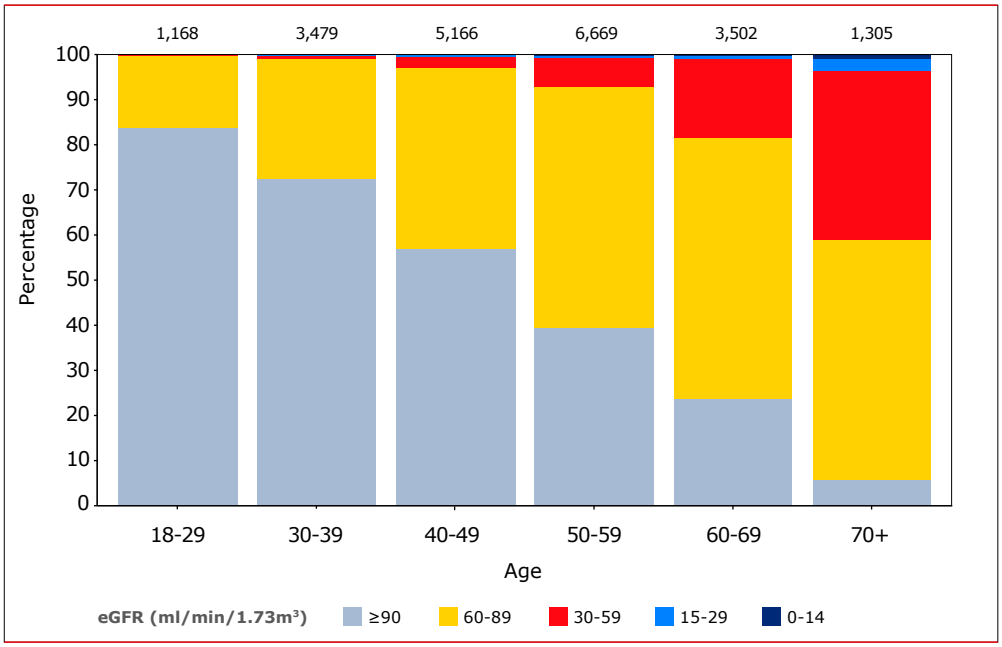
Legend: *eGFR=estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60-89 ml/min/1.73m²: mildly reduced; 30-59 ml/min/1.73m²: moderately reduced; 15-29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

Table 3.5: Crude chronic kidney disease incidence per 1,000 person years of follow up in 2008-2014, and 2015-2020, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Men		Women	
	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)
2008-2014	7.1 (6.4-7.9)	0.74 (0.66-0.82)	7.3 (5.8-9.1)	0.84 (0.66-1.02)
2015-2020	11.9 (11.1-12.8)	1 (reference)	12.7 (10.8-14.8)	1 (reference)

** Standardised according to the observed age distribution in 2015-2020.*
***Legend:** CI=confidence interval; PYFU=person years.*

Figure 3.10: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2020 for different age categories. For each individual, the last available measurement in 2019 was selected. The numbers at the top of each bar represent the number of individuals contributing data to that age category.



***Legend:** eGFR=estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60-89 ml/min/1.73m²: mildly reduced; 30-59 ml/min/1.73m²: moderately reduced; 15-29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

Non-AIDS-defining malignancies

Between 2000 and 2020, 1,920 diagnoses of non-AIDS-defining malignancies in 1,771 unique individuals were recorded in SHM's database. An additional 775 patients were diagnosed with one or more non-melanoma skin cancers, but these were not included in the present analysis. *Table 3.6* shows the most common types of non-AIDS-defining cancer: lung cancer (16.9%); haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 14.2%); intestinal cancer (mainly oesophageal, gastric, intestinal, and rectal cancers, but excluding liver cancer, 13.5%); invasive anal cancer (not AIN, 11.9%); prostate cancer (9.4%); and head and neck cancers (8.3%). *Figure 3.11* shows the relative and absolute changes in types of non-AIDS-defining cancers over time. The proportion of individuals with intestinal, prostate, and renal cancer has increased over time, likely reflecting the increasing age of the study population. This is further illustrated in *Figure 3.12*, which shows the distribution of non-AIDS-defining malignancies with increasing age at cancer diagnosis.

Risk factors for non-AIDS-defining malignancies

The crude incidence of non-AIDS-defining malignancies (NADM) in men and women is shown in *Figure 3.3D*. The age-standardised incidence in men was statistically significantly lower in the period 2016-20, compared to 2000-10, and borderline significantly lower compared to 2011-15 (*Table 3.7*). This lower age-standardised incidence in men may be due to a reduction over time in risk factors such as smoking, and a higher proportion of individuals living with high CD4 cell counts. The situation for women was similar – the age-standardised incidence was (borderline significantly) lower in the period 2016-20, than in 2000-10, and to a lesser extent in 2011-15 (*Table 3.7*).

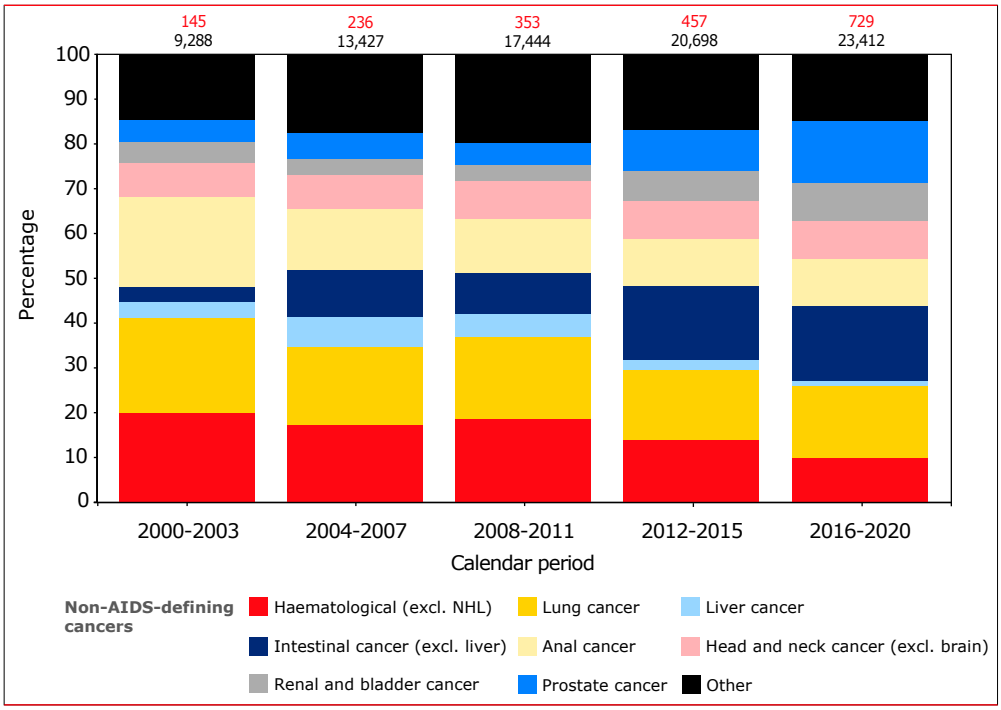
Demographic and clinical factors independently associated with an increased risk of a first non-AIDS-defining malignancy were: older age group; acquiring HIV-1 through injecting drugs or contact with blood or blood products; lower current CD4 cell count (CD4 below 350 cells/mm^3); low body mass index; prior AIDS; chronic HBV co-infection; and current or past smoking (*Appendix Table 3.6*). Furthermore, people who had been pre-treated with mono- or dual-NRTI-based regimes prior to starting cART, had an independently increased risk for NADM, compared with those who started cART while being treatment naïve (relative risk [RR] 1.22, 95% CI 1.05-1.42). Of note, independent of all other risk factors investigated, people who initiated cART within 12 months of their last negative HIV test had a significantly lower risk for NADM (RR 0.62, 95% CI 0.42-0.93) than other treatment-naive people who started cART (i.e., those who either had an unknown duration of HIV infection, or a duration of more than 12 months).

In the period from 1 January 2000 to 31 December 2020, the five-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 49.8%, compared with 73.1% for CVD, 82.6% for DM, and 86.1% for CKD (*Appendix Figure 3.1*). In the same period, the five-year survival rate of all adults newly entering care in one of the Dutch HIV treatment centres was 95.6%, and 81.9% for those newly entering care with an AIDS diagnosis. The five-year survival rates following the most common non-AIDS-defining malignancies are shown in *Table 3.6* and *Appendix Figure 3.2*.

Anal cancer

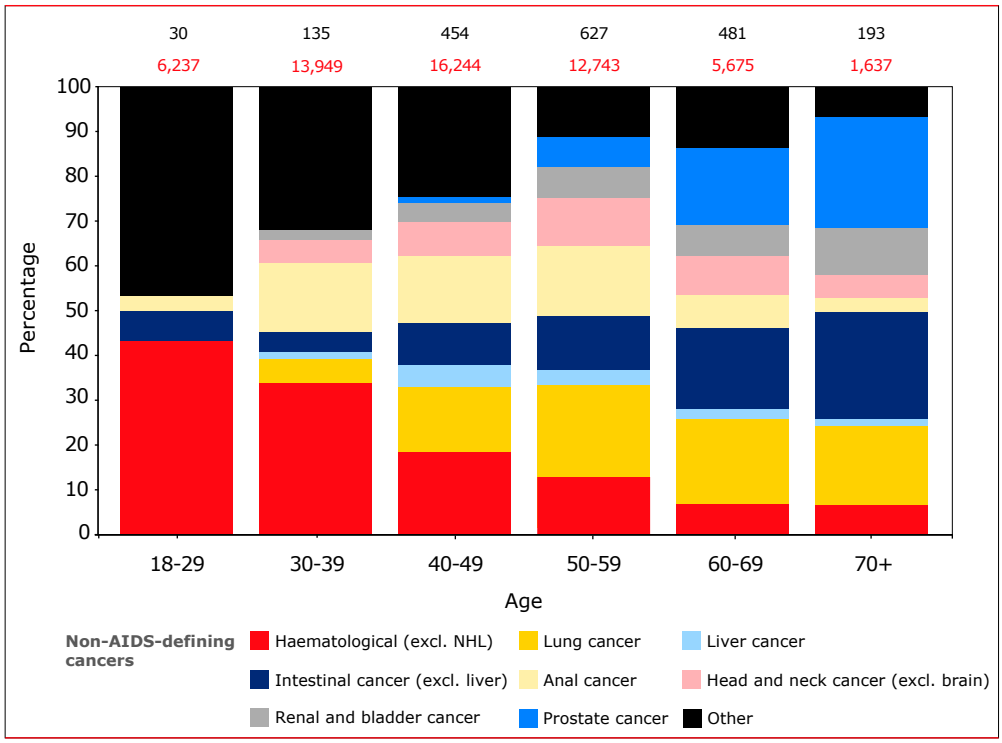
In total, 219 men living with HIV and 10 women living with HIV were diagnosed with anal cancer. Among men living with HIV, the incidence of anal cancer fluctuated between 0.4 and 1.5 cases per 1,000 PYFU between 2000 and 2020 (*Figure 3.3G*). A 2015 study exploring the incidence of anal cancer among HIV-1-positive individuals in the Netherlands showed a significantly higher incidence of anal cancer in men who have sex with men (MSM), than in heterosexual men[37]. However, in this chapter, we will not report on the trend in anal cancer among heterosexual men over time, as the number of heterosexual men with anal cancer is too small (n=23) to analyse.

Figure 3.11: Relative changes in non-AIDS-defining malignancies between 2000 and 2020 in HIV-1-positive individuals in the Netherlands. The numbers at the top of each bar represent the number of non-AIDS-defining cancer diagnoses (top number) and the total number of individuals in care during that calendar period (bottom number).



Legend: excl.=excluding; NHL=non-Hodgkin's lymphoma.

Figure 3.12: Relative changes in non-AIDS-defining malignancies with increasing age in HIV-1-positive individuals living with HIV in the Netherlands. The numbers at the top of each bar represent the number of individuals at risk and the number of cancer diagnoses in that age category between 2000 and 2020.



Legend: *excl.=excluding; NHL=non-Hodgkin's lymphoma.*

Table 3.6: Most common non-AIDS-defining malignancies diagnosed in 2000-2020, excluding non-melanoma skin cancer and pre-malignant lesions found by cervical and anal screening.

Non-AIDS malignancy	Number of malignancies	%	5-year survival (%)
Lung cancer	325	16.9	15.0
Hematological (excl. NHL)	272	14.2	64.7
Intestinal cancer (excl. liver)	259	13.5	32.8
Anal cancer	229	11.9	65.5
Prostate cancer	181	9.4	77.6
Head and neck cancer (excl. brain)	159	8.3	57.9
Renal and bladder cancer	120	6.3	62.9
Other cancers	102	5.3	45.8
Malignant melanoma	85	4.4	72.9
Liver cancer	60	3.1	14.8
Breast cancer	50	2.6	81.6
Testicular cancer	38	2.0	87.9
Gynecological cancer (excl. cervical)	27	1.4	69.2
CNS cancer	13	0.7	64.8

***Legend:** excl.=excluding; NHL=non-Hodgkin's lymphoma.*

Table 3.7: Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up in 2000-2010, 2011-2015, and 2016-2020, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Men		Women	
	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)
2000-2010	6.6 (6.0-7.1)	1.29 (1.18-1.39)	3.2 (2.5-4.0)	1.26 (0.97-1.55)
2011-2015	6.6 (6.0-7.2)	1.01 (0.92-1.10)	4.3 (3.4-5.5)	1.13 (0.87-1.40)
2016-2020	7.9 (7.3-8.6)	1 (reference)	4.9 (3.9-6.0)	1 (reference)

** Standardised according to the observed age distribution in 2011-2020.*

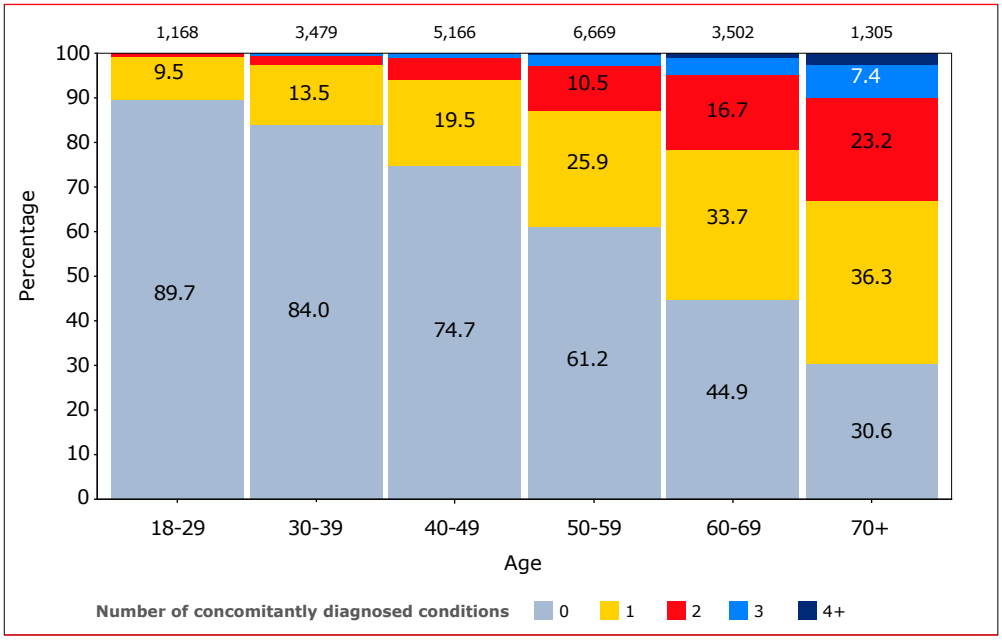
***Legend:** CI=confidence intervals; PY=person years*

Multimorbidity

We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infections and AIDS diagnoses did not contribute to the multimorbidity count. The following comorbidities and conditions were taken into account: (1) cardiovascular disease (either myocardial infarction, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy); (2) stroke; (3) non-AIDS-defining malignancies, excluding non-melanoma skin cancers and pre-malignant lesions found at cervical/anal screening; (4) chronic kidney disease (eGFR below 30 ml/min/1.73 m^2); (5) diabetes mellitus (according to D:A:D diagnostic criteria); (6) hypertension, defined as the use of antihypertensive drugs and/or measured grade 2 (or higher) hypertension with systolic pressure at or above 60 mmHg and/or diastolic pressure at or above 100 mmHg; and (7) obesity (BMI over 30). Note that more stringent definitions of CKD and hypertension have been applied here than in the analyses presented earlier in this chapter; this is to avoid overdiagnosis of CKD in people using antiretroviral drugs that inhibit tubular secretion of creatinine, and hypertension in those with borderline hypertension. Recurrences and non-primary CVD, stroke, and non-AIDS-defining malignancy events were not considered. Finally, CKD, hypertension, and obesity could be reversible.

Appendix Figure 3.4 shows the prevalence of each individual comorbidity over calendar time. *Figure 3.13* shows the distribution of the number of concomitantly-diagnosed conditions in various age categories of the adult population in 2020. The number of concomitant conditions was slightly higher in women than in men for all age categories (*Appendix Figure 3.3*). Moreover, although the average number of concomitant conditions has steadily increased over the past ten years due to the increasing average age of the cohort, the prevalence of multimorbidity by age category has remained stable over the same period (*Appendix Figure 3.5*). After adjusting for the variables listed in *Appendix Table 3.2*, multimorbidity was independently associated with increased risk of mortality (RR 2.20, 95% CI 2.12-2.30, $p<0.001$, per additional comorbidity diagnosed).

Figure 3.13: Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2020. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



Polypharmacy

Polypharmacy, commonly defined as the concomitant use of five or more medications, is associated with adverse health outcomes; prescription errors; lower adherence; and an increased risk of clinically relevant pharmacological interactions and adverse drug reactions, especially in the elderly. At the end of each calendar year, we count the number of registered comedications for each individual in active follow up. Antiretroviral agents are excluded from this count. We counted individual ATC codes (Anatomical Therapeutic Chemical classification system[a]) of the comedications. Note that coformulated combinations, such as cotrimoxazole, have a single ATC code and therefore increase the comedication count by one.

In 2020, 21.9% of adults in active follow up had no recorded comedication use, while 30.7%, 15.9%, 10.0%, and 6.8% used one, two, three, or four comedications, respectively. A further 14.7% used five or more non-antiretroviral comedications in addition to their cART regimen, which qualifies as polypharmacy. The prevalence

a *https://www.whocc.no/atc_ddd_index/*

of polypharmacy among adults has increased over time (*Figure 3.14*): in 2000, just 3.1% of adults used five or more non-antiretroviral comedications in addition to their cART regimen. The main drivers for this increase are the rising age of the population and the growth in the number of chronic comorbidities. Older people (*Figure 3.15A*), and those with more comorbidities (*Figure 3.16*), used more comedications. There were some differences between men and women, with women using slightly more comedications than men, while the most pronounced differences were to be found in the youngest age groups (*Figure 3.15B*). Finally, in adults using cART in the period 2007-20, polypharmacy was also associated with an increased risk of death (RR 2.23, 95% CI 2.00-2.49, $p<0.001$), independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities (i.e., multimorbidity). All co-medications used by at least 250 adults living with HIV in care in 2020 are listed in *Table 3.8*.

Table 3.8: Use of comedications in 2020.

Comedication use in 2020	n	%
ATC group		
Lipid modifying agents	4,042	8.7
Drugs for acid-related disorders	3,582	7.7
Agents acting on the renin-angiotensin system	3,052	6.6
Antithrombotic agents	2,601	5.6
Psycholeptics drugs (antipsychotics, anxiolytics, hypnotics, sedatives)	2,181	4.7
Psychoanaleptics (antidepressants, psychostimulants)	2,134	4.6
Mineral supplements	1,998	4.3
Drugs used in diabetes	1,877	4.0
Drugs for obstructive airway diseases	1,808	3.9
Urological drugs	1,604	3.5
Beta blocking agents	1,584	3.4
Calcium channel blockers	1,352	2.9
Antibacterial drugs	1,082	2.3
Sex hormones and modulators of the genital system	1,080	2.3
Diuretic drugs	1,022	2.2
Antianaemic drugs	1,007	2.2
Analgesic drugs	815	1.8
Antiepileptic drugs	781	1.7
Corticosteroids systemic	771	1.7
Antiviral drugs	721	1.6
Cardiac therapy	634	1.4
Nasal preparations	558	1.2
Topical dermatological corticosteroids	508	1.1
Antimycotic drugs	450	1.0
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents	444	1.0
Drugs affecting bone structure and mineralisation	405	0.9
Thyroid therapy	333	0.7

Figure 3.14: Number of comedications used over calendar time. The numbers at the top of each bar represent the number of individuals contributing data to that period. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per period.

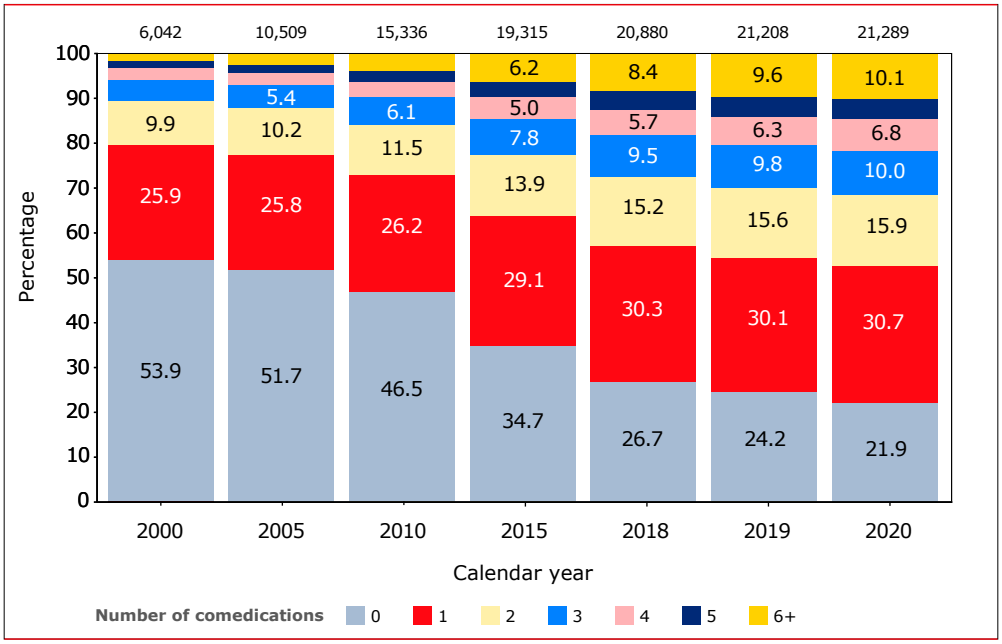
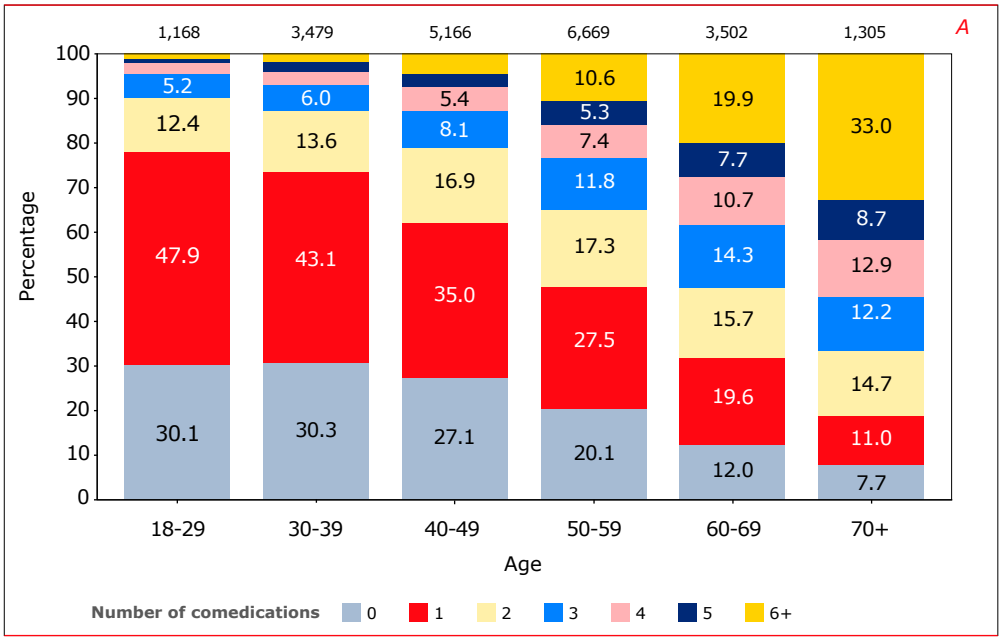


Figure 3.15: Number of comedications used by (A) age group, and (B) gender in 2020. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



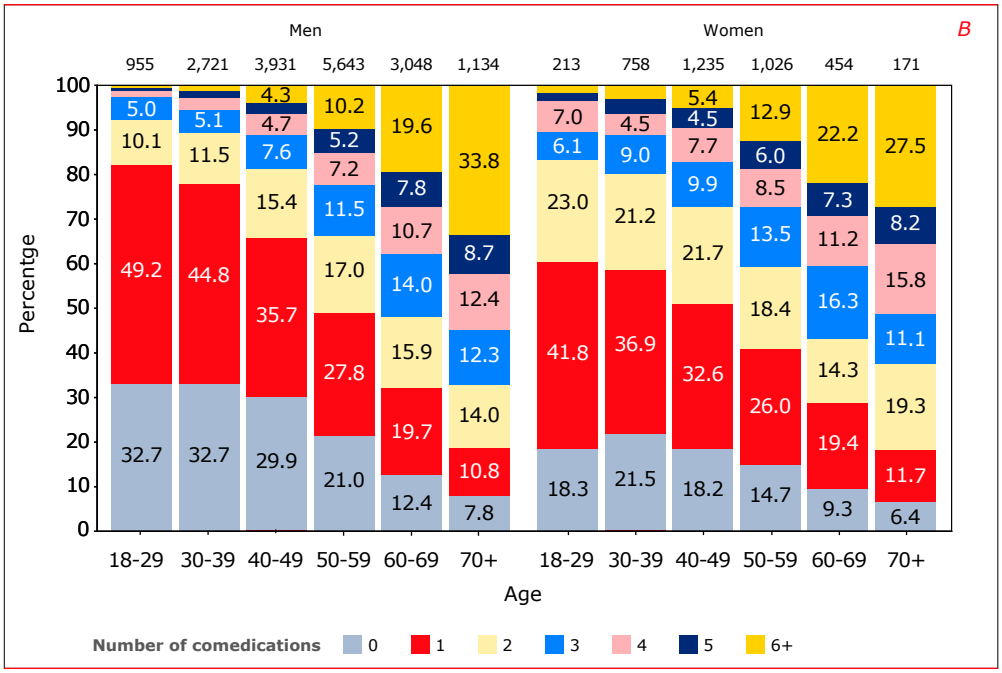
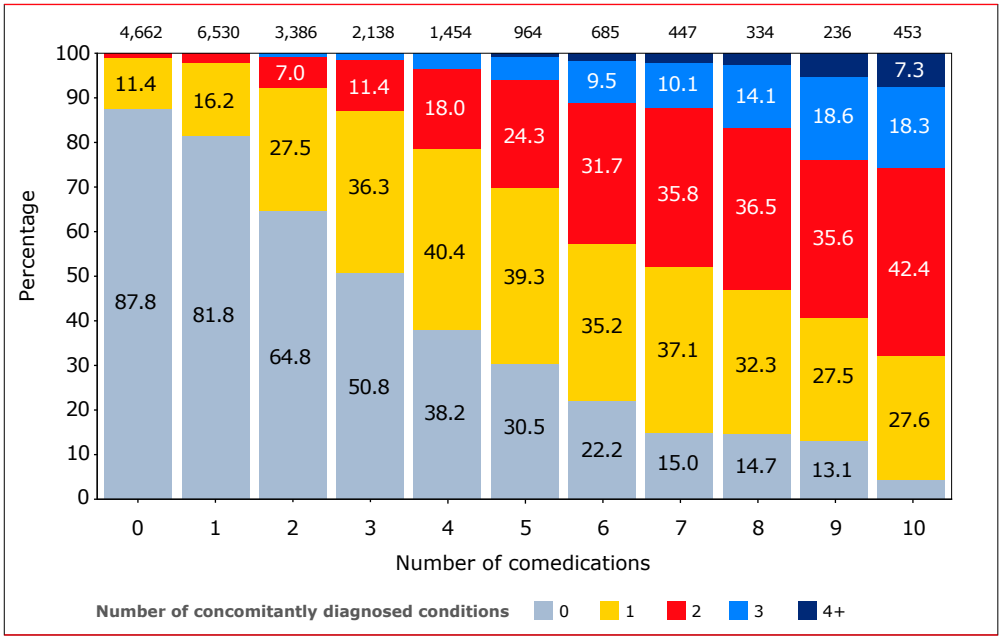


Figure 3.16: Number of comedications used in relation to the number of prevalent comorbidities. The numbers at the top of each bar represent the number of individuals contributing data to that category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per category.



Summary and conclusions

AIDS, mortality, and causes of death

AIDS-related deaths have decreased dramatically since cART became available in the Netherlands in 1996. The limited number of deaths from AIDS each year mainly occur among those who present late for care with already advanced immunodeficiency. The five-year survival rate after a first AIDS-defining condition is far greater than after a diagnosis of cardiovascular disease (CVD), or a non-AIDS-defining malignancy. Death is increasingly likely to be the result of a non-AIDS cause, with non-AIDS malignancies and CVD being the most common. This not only reflects the increased risk of non-AIDS morbidity in individuals with more advanced HIV infection, but also the continuously increasing age of the population of individuals in care. As a result, on average, the mortality rate among people living with HIV in the Netherlands remains substantially higher than in the general Dutch population, although it is slowly approaching the general Dutch

population rate. Furthermore, several studies have found that mortality rates in individuals on treatment who achieve CD4 counts above 500 cells/mm^3 may even drop below general population rates[38,39].

Diabetes and cardiovascular disease

Whereas the crude incidence of diabetes mellitus and CVD in men and women was found to have remained relatively stable, the age-standardised incidence for CVD declined over time in men and women, while the age-adjusted incidence for diabetes mellitus only declined in men. This decline may suggest improved awareness, prevention (including switching from drugs associated with an increased risk of diabetes mellitus[40] and myocardial infarction[41,42]), and increased attention to managing traditional risk factors for these conditions. It may also reflect an increasing proportion of individuals living at high CD4 cell counts (because of the trend over time to start cART at higher CD4 cell counts, but also due to an increase in the proportion of individuals who have used cART long enough to reach high CD4 cell counts). The observation that the age-standardised incidence ratios for diabetes mellitus do not decline as much in women remains unexplained and needs further study – but the observed increasing average BMI and high prevalence of obesity in women might partially explain this observation. Finally, the risk factors observed for diabetes mellitus and CVD (including age, hypertension, smoking, and obesity), were similar to those previously reported in other studies[40,43,44]. Several of these risk factors are more prevalent among people living with HIV[19].

Cardiovascular risk factors

The proportion of adults living with HIV at high (5-10%), or very high (more than 10%) cardiovascular risk slowly increased from 11.7% and 5.6%, respectively, in 2000, to 20.4% and 12.1%, respectively, in 2020. This increase largely reflects the increased average age of the population. We observed that cardiovascular risk management has improved over time, as illustrated by the increasing use of statins and antihypertensives, and the shift away from the use of antiretrovirals that have been demonstrated to be associated with increased cardiovascular risk, particularly in individuals with high underlying risk[45] (*Chapter 2*). Significant room for further improvement remains, however, particularly given the suboptimal use of statin therapy, antihypertensive therapy, and low-dose acetylsalicylic acid as secondary prevention following a myocardial infarction or ischaemic stroke, and the low, albeit slowly improving, uptake of these medications in the prevention of primary cardiovascular disease. The increased availability of preferred antiretroviral treatment options that do not contain pharmacological boosters that can interfere with these preventive medicines has made it easier to implement proper cardiovascular risk management.

The clinical significance of the increase in BMI over time, especially in women, requires further study. Recent results suggest that weight gain after starting cART is associated with lower mortality for normal-weight individuals, but they show no clear benefit for overweight or obese individuals[46]. However, another study found that weight gain after starting cART was associated with an increased risk of diabetes, and, in those with a pre-antiretroviral therapy BMI in the normal range, with an increased risk of cardiovascular disease[47]. Prospective longitudinal monitoring of lipid levels; smoking status; blood pressure; weight; and other risk factors will be important to further optimise the assessment of cardiovascular risk in our increasingly ageing HIV-1-positive population, and to study the impact of interventions, such as the use of statins and antihypertensive therapy, in modifying disease risk. In our cohort, we found that obesity and being overweight were significant risk factors for developing new-onset diabetes and CKD, but not cardiovascular disease and non-AIDS malignancies. Obese and overweight adults had a significantly lower risk of death than those with an ideal body weight, although this is likely biased by reverse causality, as body weight was included as a time-updated variable in our regression analyses. Currently, analyses are underway in our cohort to look in depth at the relationship between weight gain on cART and the use of specific antiretroviral agents (the integrase strand transfer inhibitors and tenofovir alafenamide, in particular), while controlling for demographic characteristics, traditional risk factors, and confounders.

Renal insufficiency

Since 2008, there has been a steady increase in the incidence of new-onset chronic kidney disease (CKD). As expected, older individuals, and those with traditional risk factors such as hypertension, were found to be at increased risk of CKD, as were individuals with advanced immunodeficiency. In addition, other studies have also reported hepatitis B and C virus co-infection[48,49], and the use of tenofovir disoproxil fumarate, atazanavir/ritonavir, and lopinavir/ritonavir, to be additional independent predictors of chronic renal impairment[50]. Moreover, renal impairment in the population living with HIV is associated with an increased risk of cardiovascular disease[51]. The increase in CKD in our population, appears to be largely caused by the increased use of dolutegravir, bictegravir, rilpivirine, and cobicistat, all of which cause reversible inhibition of tubular excretion of creatinine, without causing a true decrease in glomerular filtration.

Non-AIDS-defining malignancies

The most common non-AIDS-defining malignancies (NADM) in the Netherlands are lung, intestinal, anal, and head and neck cancer, as well as Hodgkin's lymphoma. The crude incidence of NADM has remained stable over time, and we also observed a decline in age-standardised incidence of NADM in men, and to a lesser extent in women. In addition, our analyses showed that individuals diagnosed with NADM a more likely to be older. This is in line with data from other cohorts, including the Swiss HIV cohort[49-52]. Additional risk factors for NADM identified in our analyses were: current or past smoking; a CD4 count below 350 cells/mm^3; not being on cART, or having been pre-treated with NRTI before the start of cART; and a prior AIDS diagnosis. Other studies have reported that the effect of immunodeficiency may be stronger for infection-related non-AIDS-defining malignancies[56]. Importantly, individuals who had initiated cART earlier in infection (i.e., within 12 months of a last negative HIV test), had a significantly lower risk of NADM (RR 0.54, 95% CI 0.33-0.86, p=0.009), independent of other traditional and HIV-related risk factors. The five-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 50.1%.

Multimorbidity and polypharmacy

The prevalence of non-AIDS multimorbidity is slowly increasing, driven mainly by the increasing age of the cohort, and by women experiencing more comorbidities in each age group. Multimorbidity is strongly and independently associated with increased risk of mortality.

Polypharmacy, defined as the concomitant use of five or more medications in addition to cART, is becoming more prevalent, mainly because of the increased age of the cohort and the associated rise in the prevalence of age-associated, non-AIDS comorbidities. In 2000, 3.0% of adults used five or more non-antiretroviral comedications alongside their cART regimen, and this steadily increased to 14.7% of adults in active follow up in 2020. The main drivers behind this increase in polypharmacy are the increasing age of the population and the increase in the number of chronic comorbidities per individual. In adults using cART in the period 2007-20, polypharmacy was also strongly and independently associated with an increased risk of death, independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities.

Recommendations

The proportion of individuals dying of AIDS in the Netherlands has markedly declined throughout the cART era, but to reach the goal of zero AIDS-deaths by 2022, it will be imperative to identify individuals earlier after infection, and rapidly link them to care for immediate start of treatment. This can also be expected to beneficially impact the incidence of comorbidities for which advanced immunodeficiency is a contributing risk factor[54-56]. Of note, our own analyses show a markedly lower risk for non-AIDS malignancies in those who initiate cART within the first year of infection.

The relatively poor five-year survival rates following the diagnosis of several of the analysed non-AIDS-defining comorbidities, compared with survival of all people newly entering care with an AIDS diagnosis, underlines the importance of primary prevention, early diagnosis and aggressive pursuit of treatment and secondary prevention of non-AIDS comorbidities in the population living with HIV. Studies such as the ongoing Comorbidity and Aging with HIV (AGEhIV) cohort study have provided further insights into the independent contribution of HIV and HIV-associated factors, such as innate and adaptive immune and coagulation activation and inflammation. This will hopefully guide the development of interventions that target relevant pathophysiological mechanisms[9,60].

It is important to note that the risk of many, if not each, of the comorbidities frequently identified in people living with HIV, is determined by multiple factors. Besides immunodeficiency, additional key contributors for consideration include both well-known traditional unmodifiable risk factors, such as age and genetic predisposition, and modifiable lifestyle-related factors, as well as known, and potentially unknown, effects of antiretroviral treatment and co-infection. As the population of people living with HIV that is in care in the Netherlands continues to age, the comorbidity burden continues to increase. In tandem with multi-morbidity, the risk for polypharmacy is also strongly on the rise in recent years. Both multimorbidity and polypharmacy were each independently associated with an increased risk of death. Adequate prevention and management of comorbidities will become even more important as more people living with HIV are entering their 70s and 80s. Polypharmacy should also be adequately managed using tools developed in geriatric medicine (e.g., START/STOPP and Beers), to limit the risk of complex drug-drug interactions, side effects, non-adherence, and other severe adverse health outcomes.

Awareness on the part of both physicians and people living with HIV of the role of modifiable, lifestyle-related risk factors (particularly in older individuals, or those otherwise at high risk of certain comorbidities), along with the appropriate management of these risk factors, offer considerable hope for lowering the comorbidity burden and ensuring healthy ageing in people living with HIV.

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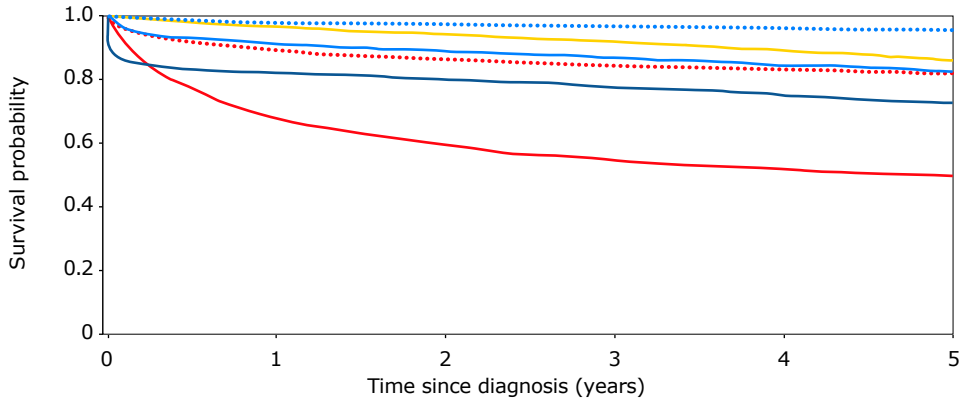
Appendix: supplementary figures and tables

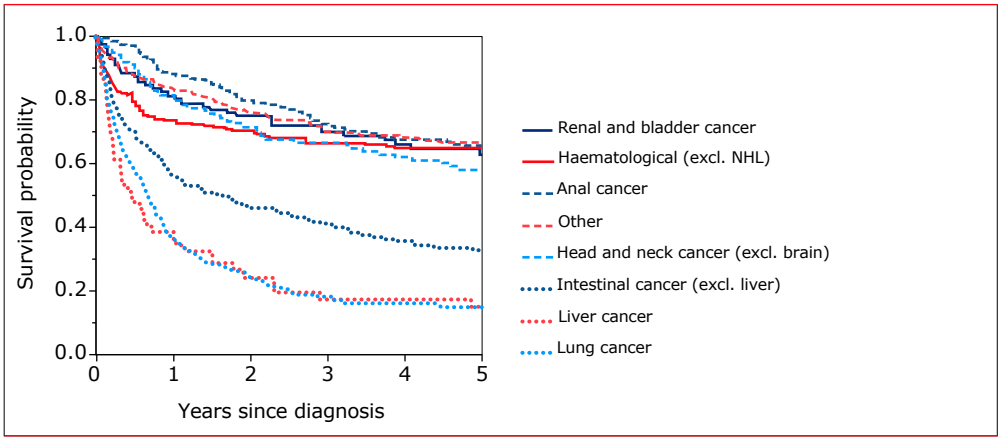
Appendix Figure 3.1: *Estimated five-year survival following the diagnosis of cardiovascular disease, non-AIDS-defining malignancy, diabetes mellitus, and chronic kidney disease. Two reference groups are included: survival from date of entry into HIV care (after 1 January 2000), and from date of first AIDS diagnosis (after 1 January 2000). The numbers below the graph represent the number of subjects per stratum at risk at each time point.*



Time since diagnosis (years)	0	1	2	3	4	5
CVD	1,616	1,258	1,116	973	859	745
NADM	1,490	966	762	616	507	422
DM	1,485	1,264	1,149	1,022	904	793
CKD	2,331	2,039	1,801	1,520	1,210	918
In care for HIV	22,348	20,524	19,211	18,017	16,837	15,714
AIDS	3,628	3,073	2,858	2,666	2,491	2,336

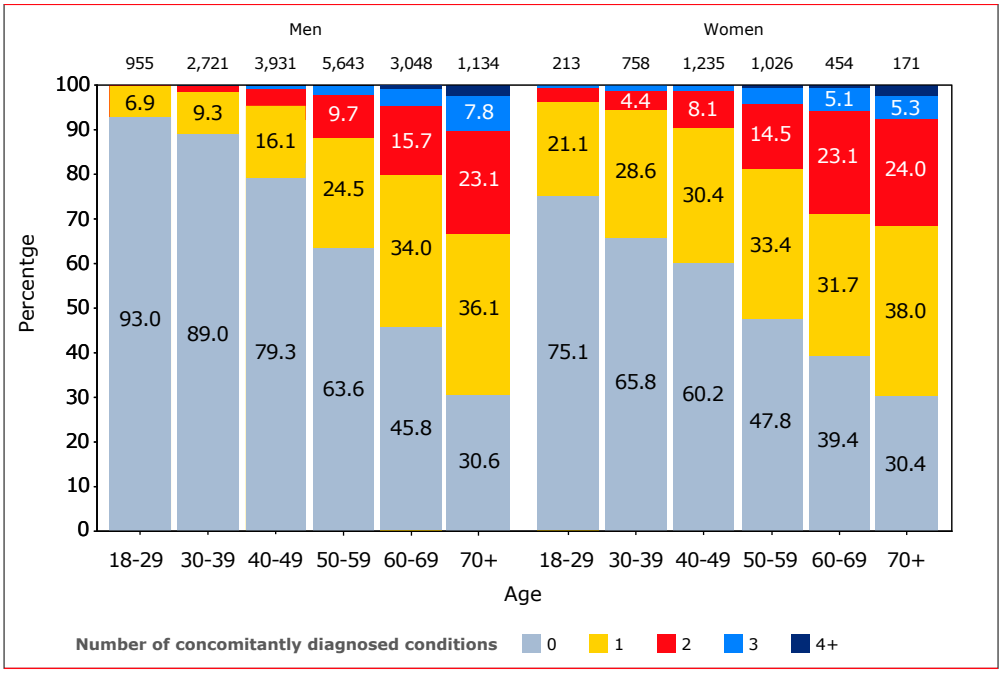
Legend: *KM=Kaplan-Meier; CVD=cardiovascular disease; NADM=non-AIDS defining malignancy; DM=diabetes mellitus; CKD=chronic kidney disease.*

Appendix Figure 3.2: *Estimated five-year survival following the diagnosis of the most common non-AIDS-defining malignancies diagnosed between 1 January 2000 and 31 December 2020.*

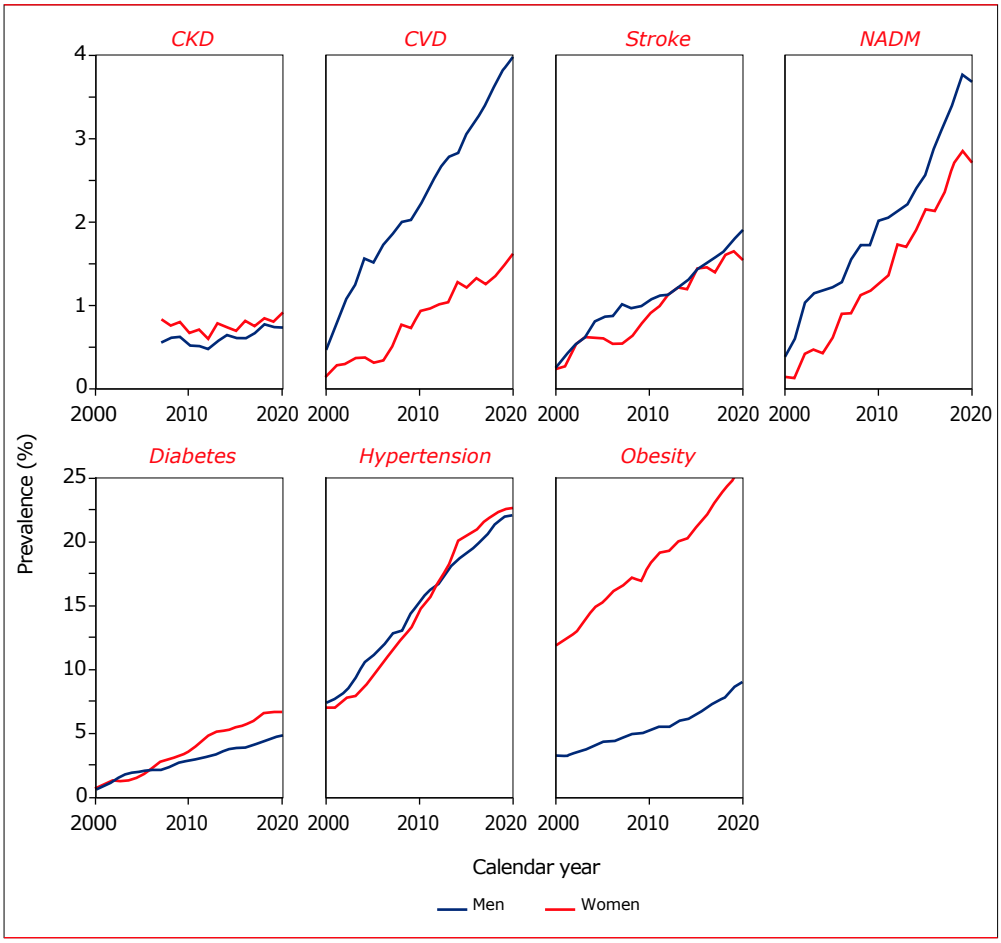


Legend: *KM=Kaplan-Meier; excl.=excluding; NHL=non-Hodgkin's lymphoma.*

Appendix Figure 3.3: *Prevalence of non-AIDS multimorbidity by gender in the adult population in 2020. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.*

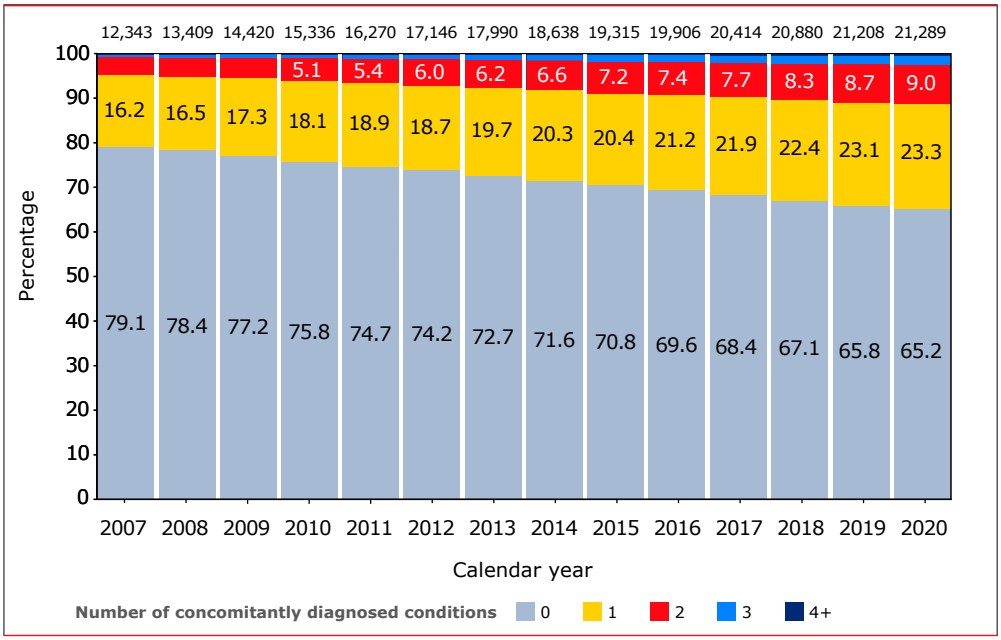


Appendix Figure 3.4: *Prevalence of non-AIDS comorbidities in the adult population between 2000 and 2020.*



Legend: *CKD=chronic kidney disease; CVD=cardiovascular disease; NADM=non-AIDS-defining malignancies.*

Appendix Figure 3.5: Prevalence of non-AIDS multimorbidity in the adult population. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per calendar year.



Appendix Table 3.1: *Absolute number of causes of death among HIV-1-positive individuals during the periods 1996-2000, 2001-2005, 2006-2010, and 2011-2020.*

	Calendar period								
Causes of death	**96-00**	**01-05**	**06-10**	**11-15**	**2016**	**2017**	**2018**	**2019**	**2020**
AIDS									
AIDS - infection	69	120	148	103	6	4	4	7	4
AIDS - malignancy	60	63	61	43	8	13	10	11	5
AIDS - unclassifiable	89	63	19	15	10	3	4	5	4
Subtotal	*218*	*246*	*228*	*161*	*24*	*20*	*18*	*23*	*13*
Non-AIDS malignancies	*30*	*95*	*136*	*193*	*49*	*62*	*48*	*75*	*60*
Cardiovascular disease									
Myocardial infarction	14	30	46	40	8	4	2	12	15
Stroke	3	11	13	11	7	3	3	2	3
Other CVD	6	24	26	50	16	10	16	12	13
Subtotal	*23*	*65*	*85*	*101*	*31*	*17*	*21*	*26*	*31*
Non-AIDS infection	*23*	*42*	*32*	*27*	*7*	*3*	*10*	*6*	*14*
Liver disease	*15*	*28*	*55*	*43*	*6*	*7*	*8*	.	*1*
Lung disease	*7*	*11*	*30*	*38*	*13*	*14*	*9*	*15*	*6*
Non-natural death									
Accident or violence	6	11	22	16	7	2	4	1	1
Suicide	12	30	30	52	10	12	11	4	12
Euthanasia	7	5	.	2	1	.	.	.	.
Subtotal	*25*	*46*	*52*	*70*	*18*	*14*	*15*	*5*	*13*
Alcohol and substance abuse	12	15	27	18	10	4	4	2	4
Other causes	21	24	23	43	13	8	18	10	11
Unknown	23	57	53	84	20	18	21	12	11
Total	**397**	**629**	**721**	**778**	**191**	**167**	**172**	**174**	**164**

Legend: *CVD=cardiovascular disease.*

Appendix Table 3.2: Adjusted risk factors for death and AIDS among HIV-1-positive individuals.

			Death			AIDS
	RR (95% CI)	p-value	Overall p-value	RR (95% CI)	p-value	Overall p-value
Risk factors						
Male gender	1.28 (1.12-1.47)	<.001		0.96 (0.82-1.13)	0.655	
Region of birth						
Netherlands	1 (reference)		0.140	1 (reference)		0.098
Other	0.93 (0.84-1.02)	0.142		1.10 (0.98-1.24)	0.098	
HIV-1 transmission route						
Blood contact	0.77 (0.55-1.06)	0.111		0.85 (0.59-1.22)	0.385	
Heterosexual	1.05 (0.94-1.19)	0.392		0.90 (0.77-1.04)	0.147	
IDU	1.61 (1.34-1.94)	<.001		0.72 (0.56-0.93)	0.013	
MSM	1 (reference)		<.001	1 (reference)		0.031
Age*						
18-29	0.90 (0.65-1.24)	0.506	<.001	1.08 (0.88-1.33)	0.449	<.001
30-39	1 (reference)			1 (reference)		
40-49	1.50 (1.29-1.75)	<.001		1.09 (0.95-1.24)	0.218	
50-59	2.65 (2.28-3.08)	<.001		1.34 (1.16-1.56)	<.001	
60-69	4.78 (4.07-5.61)	<.001		1.39 (1.15-1.68)	<.001	
70+	10.50 (8.72-12.64)	<.001		2.04 (1.48-2.81)	<.001	
CD4 cell count**						
0-50	14.20 (11.83-17.05)	<.001	<.001	6.74 (5.39-8.42)	<.001	<.001
50-199	5.06 (4.42-5.80)	<.001		2.82 (2.39-3.34)	<.001	
200-349	2.14 (1.87-2.45)	<.001		1.64 (1.40-1.93)	<.001	
350-499	1.38 (1.21-1.58)	<.001		1.26 (1.07-1.49)	0.006	
500-749	1 (reference)			1 (reference)		
750+	0.86 (0.74-0.99)	0.040		1.15 (0.95-1.39)	0.151	
Per year longer on cART with HIV RNA >1,000 copies/ml	1.05 (1.03-1.07)	<.001	<.001	1.03 (1.01-1.06)	0.018	0.020
Treatment status at start cART						
Treatment-experienced	0.96 (0.87-1.06)	0.446		0.63 (0.55-0.72)	<.001	
Treatment-naive	1 (reference)			1 (reference)		
Prior AIDS event	1.73 (1.58-1.89)	<.001				
Hepatitis B virus positive	1.26 (1.10-1.44)	0.001		1.13 (0.93-1.37)	0.221	
Hepatitis C virus positive	1.58 (1.37-1.83)	<.001		1.23 (1.02-1.48)	0.027	

	Death			AIDS		
	RR (95% CI)	p-value	Overall p-value	RR (95% CI)	p-value	Overall p-value
Body mass index*						
0–18	3.07 (2.70–3.49)	<.001	<.001			
18–25	1 (reference)					
25–30	0.67 (0.61–0.75)	<.001				
30+	0.86 (0.72–1.01)	0.073				
Smoking status						
Current smoker	1.10 (0.97–1.25)	0.129	<.001	0.76 (0.67–0.86)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	2.04 (1.82–2.30)	<.001		0.94 (0.81–1.09)	0.408	
Early cART***	0.86 (0.61–1.20)	0.376		1.18 (0.90–1.55)	0.232	

** Time-updated.*

*** Time-updated and lagged by three months.*

**** cART started within 12 months of the last HIV-negative test.*

***Legend:** cART=combination antiretroviral therapy; IDU=people who inject drugs; MSM=men who have sex with men; CI=confidence interval; RR=risk ratio.*

Appendix Table 3.3: *Lost to follow up (no follow up after 31 December 2019) by region of origin and time-updated CD4 cell count.*

	Total			Caribbean			Western Europe / North America		
Last CD4 count	**n**	**PY**	**Incidence/ 1,000 PY (95% CI)**	**n**	**PY**	**Incidence/ 1,000 PY (95% CI)**	**n**	**PY**	**Incidence/ 1,000 PY (95% CI)**
0–50	47	2,713	17.3 (12.7–23.0)	2	218	9.2 (1.1–33.1)	8	177	45.2 (19.5–89.0)
050–199	199	9,866	20.2 (17.5–23.2)	12	726	16.5 (8.5–28.9)	35	1,068	32.8 (22.8–45.6)
200–349	415	22,053	18.8 (17.1–20.7)	16	1,058	15.1 (8.6–24.6)	83	1,901	43.7 (34.8–54.1)
350–499	562	43,264	13.0 (11.9–14.1)	37	1,821	20.3 (14.3–28.0)	125	3,699	33.8 (28.1–40.3)
500–749	816	93,993	8.7 (8.1–9.3)	60	4,533	13.2 (10.1–17.0)	202	7,640	26.4 (22.9–30.3)
750+	563	107980	5.2 (4.8–5.7)	43	5,409	7.9 (5.8–10.7)	171	9,545	17.9 (15.3–20.8)

Legend: *n=number; PY=person years of follow up; CI=confidence interval.*

	Netherlands			Sub-Saharan Africa			South and south-east Asia		
	n	PY	Incidence/ 1,000 PY (95% CI)	n	PY	Incidence/ 1,000 PY (95% CI)	n	PY	Incidence/ 1,000 PY (95% CI)
	4	1,755	2.3 (0.6–5.8)	27	445	60.6 (40.0–88.2)	6	117	51.3 (18.8–111.6)
	31	5,983	5.2 (3.5–7.4)	110	1,757	62.6 (51.5–75.5)	11	333	33.0 (16.5–59.1)
	82	13,985	5.9 (4.7–7.3)	208	4,330	48.0 (41.7–55.0)	26	781	33.3 (21.8–48.8)
	128	28,324	4.5 (3.8–5.4)	250	7,598	32.9 (28.9–37.2)	22	1,822	12.1 (7.6–18.3)
	251	63,147	4.0 (3.5–4.5)	281	14,626	19.2 (17.0–21.6)	22	4,047	5.4 (3.4–8.2)
	201	77,065	2.6 (2.3–3.0)	130	12,500	10.4 (8.7–12.3)	18	3,461	5.2 (3.1–8.2)

Appendix Table 3.4: *Absolute number of first AIDS events among HIV-1-positive individuals during the periods 1996-2000, 2001-2005, 2006-2010, 2011-2015 and 2016-2020.*

CDC event	1996-2000	2001-2005	2006-2010	2011-2015	2016-2020	Total	
	n	n	n	n	n	n	%
AIDS dementia complex - HIV encefalopathy	37	47	51	44	18	197	2.95
Bacterial pneumonia, recurring	48	64	66	77	88	343	5.14
CMV colitis/proctitis	1	.	1	1	3	6	0.09
CMV disease	26	35	29	33	3	126	1.89
CMV meningo-encefalitis	.	.	.	.	1	1	0.01
CMV pneumonitis	.	.	.	.	11	11	0.16
CMV retinitis	30	20	12	12	10	84	1.26
Candidiasis lungs/bronchial/trachea	7	13	7	6	7	40	0.60
Candidiasis oesophagitis	260	238	251	223	134	1106	16.56
Cervical cancer, invasive	3	4	6	4	4	21	0.31
Coccidioimycosis, extrapulmonary / disseminated	.	.	1	.	.	1	0.01
Cryptococcosis, extrapulmonary / disseminated	21	31	33	11	11	107	1.60
Cryptosporidiosis	22	12	11	12	2	59	0.88
Cystoisosporiasis	3	9	6	.	.	18	0.27
HIV wasting	50	57	77	78	57	319	4.78
HSV chronic ulcer	1	1	1	3	18	24	0.36
HSV oesophagitis	.	.	.	.	1	1	0.01
HSV pneumonitis	.	.	.	.	1	1	0.01
Herpes simplex virus	32	41	59	37	9	178	2.67
Histoplasmosis, extrapulmonary / disseminated	9	12	10	7	2	40	0.60
Kaposi's sarcoma	153	153	187	139	85	717	10.74
Leishmaniasis visceral	.	1	2	2	2	7	0.10
Microsporidiosis	11	1	3	1	.	16	0.24
Mycobacterium avium/kansasii, extrapulmonary / disseminated	25	19	28	9	7	88	1.32
Mycobacterium avium/kansasii, pulmonary	1	2	.	1	7	11	0.16
Mycobacterium other / unspecified, extrapulmonary / disseminated	20	13	8	10	3	54	0.81
Mycobacterium other / unspecified, pulmonary	.	3	4	9	4	20	0.30
Non-Hodgkin`s lymphoma (NHL)	58	86	80	94	60	378	5.66
Penicilliosis	.	.	1	.	.	1	0.01
Pneumocystis jirovecii extrapulmonary	1	1	3	.	1	6	0.09
Pneumocystis jirovecii pneumonia	334	300	325	263	184	1406	21.06
Primary CNS lymphoma	8	4	9	6	4	31	0.46

CDC event	1996–2000	2001–2005	2006–2010	2011–2015	2016–2020	Total	
	n	n	n	n	n	n	%
Progressive multifocal leucoencefalopathy	18	25	35	24	7	109	1.63
Salmonella sepsis, recurring	2	.	.	1	.	3	0.04
Toxoplasmosis of the brain	70	97	55	42	26	290	4.34
Tuberculosis, extrapulmonary / disseminated	79	111	80	53	23	346	5.18
Tuberculosis, pulmonary	104	175	116	73	43	511	7.65
Total	**1434**	**1575**	**1557**	**1275**	**836**	**6677**	**100.00**

Legend: *CDC=Centers for Disease Control and Prevention; CMV=cytomegalovirus; MAI=mycobacterium avium intracellulare complex.*

Appendix Table 3.5: Adjusted risk factors for non-AIDS-defining morbidity.

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
Male gender	1.26 (1.13-1.41)	<.001	.	1.71 (1.41-2.07)	<.001	.
Region of birth						
Netherlands	1 (reference)	.	0.049	1 (reference)	.	0.165
Other	1.08 (1.00-1.16)	0.049	.	0.92 (0.82-1.04)	0.167	.
HIV-1 transmission route						
MSM	1 (reference)	.	<.001	1 (reference)	.	0.021
Heterosexual	1.19 (1.09-1.30)	<.001	.	1.20 (1.05-1.39)	0.010	.
IDU	1.33 (1.10-1.61)	0.004	.	1.20 (0.88-1.63)	0.240	.
Blood contact	1.26 (0.99-1.61)	0.060	.	1.18 (0.80-1.74)	0.414	.
Age*						
18-29	0.61 (0.46-0.80)	<.001	<.001	0.51 (0.28-0.94)	0.032	<.001
30-39	1 (reference)	.	.	1 (reference)	.	.
40-49	2.00 (1.76-2.26)	<.001	.	2.69 (2.11-3.42)	<.001	.
50-59	3.69 (3.25-4.19)	<.001	.	5.86 (4.62-7.44)	<.001	.
60-69	6.34 (5.52-7.27)	<.001	.	9.76 (7.60-12.55)	<.001	.
70+	10.30 (8.67-12.22)	<.001	.	16.98 (12.74-22.62)	<.001	.
CD4 cell count**						
0-50	3.99 (3.10-5.13)	<.001	<.001	3.26 (2.10-5.05)	<.001	<.001
050-199	1.81 (1.56-2.11)	<.001	.	1.64 (1.28-2.09)	<.001	.
200-349	1.28 (1.15-1.43)	<.001	.	1.34 (1.13-1.59)	<.001	.
350-499	1.05 (0.95-1.15)	0.327	.	1.06 (0.91-1.23)	0.465	.
500-749	1 (reference)	.	.	1 (reference)	.	.
750+	1.14 (1.04-1.24)	0.004	.	1.22 (1.07-1.40)	0.004	.
Per year longer with CD4<200 cells/mm^3	0.99 (0.97-1.01)	0.498	.	1.00 (0.97-1.04)	0.846	.
Prior AIDS event	1.21 (1.13-1.30)	<.001	.	1.13 (1.01-1.26)	0.041	.
Per year longer on cART while HIV RNA>1000 cp/mL	1.02 (1.00-1.04)	0.073	.	1.02 (0.99-1.05)	0.184	.
Treatment status						
Not (yet) started cART	1.17 (1.02-1.33)	0.024	<.001	1.01 (0.80-1.28)	0.915	0.013
Treatment-experienced at start cART	1.29 (1.18-1.41)	<.001	.	1.24 (1.08-1.43)	0.003	.
Treatment-naive at start	1 (reference)	.	.	1 (reference)	.	.
Per year longer on cART	1.01 (1.00-1.02)	0.025	.	1.00 (0.99-1.02)	0.632	.
Early cART within 12 months after last HIV-negat	0.83 (0.66-1.03)	0.089	.	1.08 (0.80-1.47)	0.611	.

Non-AIDS-defining malignancy			Diabetes mellitus			CKD		
IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
1.07 (0.89-1.29)	0.463	.	1.28 (1.09-1.51)	0.003	.	0.62 (0.54-0.72)	<.001	.
1 (reference)	.	0.052	1 (reference)	.	<.001	1 (reference)	.	<.001
0.88 (0.78-1.00)	0.053	.	1.49 (1.32-1.68)	<.001	.	0.77 (0.69-0.86)	<.001	.
1 (reference)	.	0.060	1 (reference)	.	<.001	1 (reference)	.	0.072
0.98 (0.84-1.14)	0.762	.	1.46 (1.26-1.69)	<.001	.	0.99 (0.87-1.13)	0.915	.
1.33 (0.99-1.80)	0.059	.	1.59 (1.14-2.23)	0.007	.	1.45 (1.10-1.91)	0.009	.
1.51 (1.06-2.14)	0.022	.	1.64 (1.14-2.35)	0.008	.	1.29 (0.94-1.78)	0.111	.
0.65 (0.39-1.09)	0.104	<.001	0.64 (0.44-0.94)	0.024	<.001	0.27 (0.11-0.68)	0.006	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
2.25 (1.78-2.84)	<.001	.	1.50 (1.25-1.80)	<.001	.	3.16 (2.35-4.24)	<.001	.
4.18 (3.31-5.27)	<.001	.	2.37 (1.96-2.86)	<.001	.	8.63 (6.49-11.47)	<.001	.
8.74 (6.86-11.14)	<.001	.	3.79 (3.07-4.68)	<.001	.	23.80 (17.88-31.68)	<.001	.
15.01 (11.36-19.84)	<.001	.	4.36 (3.23-5.89)	<.001	.	44.21 (32.63-59.88)	<.001	.
3.04 (1.89-4.88)	<.001	<.001	6.01 (4.19-8.62)	<.001	<.001	1.09 (0.49-2.46)	0.829	<.001
2.05 (1.61-2.61)	<.001	.	1.80 (1.39-2.32)	<.001	.	1.72 (1.36-2.17)	<.001	.
1.37 (1.15-1.63)	<.001	.	1.14 (0.94-1.37)	0.181	.	1.21 (1.04-1.41)	0.016	.
1.09 (0.94-1.27)	0.271	.	1.00 (0.85-1.17)	0.952	.	1.03 (0.91-1.17)	0.637	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.90 (0.78-1.05)	0.173	.	1.32 (1.15-1.52)	<.001	.	0.96 (0.86-1.08)	0.526	.
0.99 (0.95-1.02)	0.377	.	0.99 (0.96-1.03)	0.688	.	0.99 (0.96-1.01)	0.312	.
1.19 (1.06-1.34)	0.004	.	1.31 (1.16-1.47)	<.001	.	1.14 (1.03-1.26)	0.009	.
1.00 (0.97-1.03)	0.915	.	1.02 (0.99-1.05)	0.239	.	0.97 (0.94-1.00)	0.070	.
1.20 (0.96-1.51)	0.114	0.011	1.42 (1.14-1.75)	0.001	<.001	0.41 (0.28-0.59)	<.001	<.001
1.22 (1.05-1.42)	0.008	.	1.31 (1.11-1.53)	<.001	.	1.16 (1.01-1.33)	0.033	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.00 (0.99-1.02)	0.654	.	1.01 (0.99-1.02)	0.312	.	0.98 (0.98-0.99)	0.002	.
0.62 (0.42-0.93)	0.020	.	0.70 (0.45-1.09)	0.111	.	0.99 (0.79-1.25)	0.928	.

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
Body mass index*						
0-18	1.44 (1.19-1.75)	<.001	<.001	1.23 (0.90-1.67)	0.195	0.006
18-25	1 (reference)	.	.	1 (reference)	.	.
25-30	1.22 (1.12-1.32)	<.001	.	1.02 (0.91-1.16)	0.693	.
30+	1.97 (1.77-2.19)	<.001	.	1.17 (0.97-1.42)	0.100	.
Hepatitis B virus positive	1.20 (1.07-1.36)	0.003	.	1.02 (0.83-1.25)	0.827	.
Hepatitis C virus positive	1.04 (0.92-1.18)	0.508	.	1.04 (0.86-1.26)	0.689	.
Hypertension	1.14 (1.07-1.22)	<.001	.	1.20 (1.08-1.34)	<.001	.
Smoking status						
Current smoker	1.40 (1.29-1.52)	<.001	<.001	1.83 (1.60-2.08)	<.001	<.001
Never smoker	1 (reference)	.	.	1 (reference)	.	.
Past smoker	1.46 (1.34-1.60)	<.001	.	1.53 (1.32-1.76)	<.001	.
Calendar year period						
2000-2010	1.30 (1.18-1.44)	<.001	<.001	1.50 (1.29-1.75)	<.001	<.001
2011-2015	1.18 (1.08-1.28)	<.001	.	1.27 (1.11-1.45)	<.001	.
2016-2020	1 (reference)	.	.	1 (reference)	.	.
Recent use of ABC***		.	.	1.58 (1.41-1.78)	<.001	.
Per year longer on LOP/r		.	.	1.01 (0.99-1.02)	0.267	.
Per year longer on IDV		.	.	1.00 (0.99-1.01)	0.972	.
Per year longer on ZDV		.	.		.	.
Per year longer on d4T		.	.		.	.
Per year longer on ddI		.	.		.	.
Per year longer on TAF		.	.		.	.
Per year longer on TDF		.	.		.	.
Prior cardiovascular event		.	.		.	.
Prior diabetes		.	.		.	.
Current use of cobicistat		.	.		.	.
Current use of dolutegravir		.	.		.	.
Current use of rilpivirine		.	.		.	.
Current use of bictegravir		.	.		.	.

** Time-updated.*

*** Time-updated and lagged by 3 months.*

**** Current use or recently used in the past 6 months.*

Legend: *CKD=chronic kidney disease; IDU=injecting drug use; cART=combination antiretroviral therapy; LOP/r=lopinavir/ritonavir; IDV=indinavir; ABC=abacavir; ZDV=zidovudine; d4T=stavudine; ddI=didanosine; BMI: <18 kg/m²=underweight; 18-25 kg/m²=normal; 25-30 kg/m²=overweight;>30 kg/m²=severely overweight.*

	Non-AIDS-defining malignancy			Diabetes mellitus			CKD		
	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
	1.90 (1.46-2.46)	<.001	<.001	1.33 (0.91-1.96)	0.142	<.001	1.46 (1.10-1.93)	0.009	0.022
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	0.87 (0.76-0.99)	0.034	.	2.22 (1.93-2.54)	<.001	.	1.13 (1.02-1.26)	0.018	.
	0.94 (0.76-1.17)	0.594	.	5.13 (4.38-6.00)	<.001	.	1.15 (0.99-1.34)	0.076	.
	1.58 (1.32-1.89)	<.001	.	1.09 (0.88-1.34)	0.438	.	1.42 (1.20-1.68)	<.001	.
	1.09 (0.89-1.32)	0.416	.	1.00 (0.81-1.25)	0.977	.	1.33 (1.14-1.54)	<.001	.
	0.97 (0.87-1.09)	0.649	.	1.17 (1.04-1.31)	0.007	.	1.12 (1.03-1.23)	0.013	.
	1.55 (1.34-1.78)	<.001	<.001	0.99 (0.86-1.14)	0.925	<.001	0.81 (0.72-0.91)	<.001	<.001
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	1.79 (1.55-2.07)	<.001	.	1.29 (1.12-1.49)	<.001	.	1.02 (0.91-1.13)	0.781	.
	0.94 (0.80-1.11)	0.467	0.743	1.46 (1.23-1.74)	<.001	<.001	1.27 (1.07-1.51)	0.006	<.001
	0.96 (0.84-1.10)	0.550	.	1.38 (1.19-1.60)	<.001	.	1.32 (1.17-1.48)	<.001	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.	1.02 (1.00-1.03)	0.020	.		.	.
		.	.	1.02 (0.99-1.05)	0.176	.		.	.
		.	.	1.06 (1.03-1.09)	<.001	.		.	.
		.	.		.	.	1.00 (0.98-1.01)	0.550	.
		.	.		.	.	1.01 (1.00-1.01)	0.159	.
		.	.		.	.	1.59 (1.37-1.85)	<.001	.
		.	.		.	.	1.30 (1.11-1.53)	0.001	.
		.	.		.	.	1.69 (1.47-1.94)	<.001	.
		.	.		.	.	3.25 (2.90-3.65)	<.001	.
		.	.		.	.	1.33 (1.11-1.59)	0.002	.
		.	.		.	.	1.89 (1.41-2.55)	<.001	.

Appendix Table 3.6: *Specific CDC-B and CDC-C (AIDS) events occurring in individuals on cART with undetectable viral load between 2000 and 2020.*

		All events		0-50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Aspergillosis, invasive pulmonary	9	0.3%	1	0.4%
	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis oropharyngeal	754	22.0%	60	26.7%
	Candidiasis vulvovaginal, frequent/persistent	54	1.6%	1	0.4%
	Cardiomyopathy, HIV-related	5	0.1%	0	0.0%
	Cardiomyopathy, with HIV-related component	14	0.4%	1	0.4%
	Cervical dysplasia	553	16.1%	7	3.1%
	Diarrhea, HIV-related >=30 days	63	1.8%	1	0.4%
	Fever e.c.i. / HIV-related	6	0.2%	0	0.0%
	HIV-associated nephropathy (HIVAN)	21	0.6%	2	0.9%
	Herpes zoster, multidermatomal	13	0.4%	0	0.0%
	Herpes zoster, recurring / multidermatomal unspecified	217	6.3%	8	3.6%
	Herpes zoster, unidermatomal recurrent	11	0.3%	2	0.9%
	Myelopathy, HIV-related	10	0.3%	0	0.0%
	Neuropathy, HIV-related	101	2.9%	1	0.4%
	Neuropathy, with HIV-related component	72	2.1%	1	0.4%
	Nocardiosis	2	0.1%	1	0.4%
	Oral Hairy Leucoplakia (OHL)	53	1.5%	1	0.4%
	Pelvic inflammatory disease	9	0.3%	0	0.0%
	Thrombocytopenia, HIV-related	101	2.9%	4	1.8%
	Thrombocytopenia, with HIV-related component	12	0.3%	2	0.9%
	Weight loss >10%, HIV-related / unknown cause	38	1.1%	1	0.4%
Subtotal		**2119**	**61.7%**	**94**	**41.8%**
CDC-C events	AIDS dementia complex - HIV encephalopathy	45	1.3%	4	1.8%
	Bacterial pneumonia, recurring	309	9.0%	13	5.8%
	CMV disease	19	0.6%	4	1.8%
	CMV esophagitis	2	0.1%	1	0.4%
	CMV retinitis	17	0.5%	4	1.8%
	Candidiasis lungs/bronchial/trachea	10	0.3%	2	0.9%
	Candidiasis esophagitis	233	6.8%	24	10.7%
	Cervical cancer, invasive	10	0.3%	1	0.4%
	Coccidioimycosis, extrapulmonary / disseminated	1	0.0%	0	0.0%
	Cryptococcosis, extrapulmonary / disseminated	16	0.5%	6	2.7%
	Cryptosporidiosis	10	0.3%	4	1.8%
	Cystoisosporiasis	1	0.0%	0	0.0%

CD4 category										
050–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
3	0.5%	0	0.0%	1	0.2%	2	0.3%	2	0.4%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
191	29.9%	151	21.0%	123	18.6%	136	18.4%	93	20.7%
5	0.8%	7	1.0%	17	2.6%	19	2.6%	5	1.1%
1	0.2%	1	0.1%	2	0.3%	0	0.0%	1	0.2%
3	0.5%	1	0.1%	2	0.3%	5	0.7%	2	0.4%
54	8.5%	125	17.4%	108	16.4%	152	20.5%	107	23.8%
4	0.6%	19	2.6%	12	1.8%	19	2.6%	8	1.8%
1	0.2%	2	0.3%	0	0.0%	1	0.1%	2	0.4%
4	0.6%	3	0.4%	4	0.6%	3	0.4%	5	1.1%
2	0.3%	4	0.6%	2	0.3%	2	0.3%	3	0.7%
25	3.9%	51	7.1%	44	6.7%	56	7.6%	33	7.3%
0	0.0%	0	0.0%	2	0.3%	3	0.4%	4	0.9%
4	0.6%	1	0.1%	1	0.2%	1	0.1%	3	0.7%
7	1.1%	16	2.2%	28	4.2%	29	3.9%	20	4.5%
8	1.3%	11	1.5%	15	2.3%	26	3.5%	11	2.4%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
14	2.2%	10	1.4%	10	1.5%	10	1.4%	8	1.8%
0	0.0%	4	0.6%	0	0.0%	3	0.4%	2	0.4%
18	2.8%	21	2.9%	21	3.2%	25	3.4%	12	2.7%
1	0.2%	4	0.6%	0	0.0%	4	0.5%	1	0.2%
5	0.8%	10	1.4%	6	0.9%	10	1.4%	6	1.3%
351	**54.9%**	**442**	**61.5%**	**398**	**60.3%**	**506**	**68.4%**	**328**	**73.1%**
7	1.1%	9	1.3%	11	1.7%	7	0.9%	7	1.6%
53	8.3%	73	10.2%	80	12.1%	62	8.4%	28	6.2%
3	0.5%	3	0.4%	6	0.9%	1	0.1%	2	0.4%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
4	0.6%	5	0.7%	3	0.5%	1	0.1%	0	0.0%
1	0.2%	4	0.6%	1	0.2%	1	0.1%	1	0.2%
54	8.5%	56	7.8%	37	5.6%	37	5.0%	25	5.6%
2	0.3%	1	0.1%	2	0.3%	4	0.5%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
6	0.9%	2	0.3%	1	0.2%	1	0.1%	0	0.0%
0	0.0%	1	0.1%	3	0.5%	1	0.1%	1	0.2%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
	HIV wasting	16	0.5%	4	1.8%
	HSV chronic ulcer	23	0.7%	1	0.4%
	HSV pneumonitis	1	0.0%	0	0.0%
	Herpes simplex virus	62	1.8%	7	3.1%
	Histoplasmosis, extrapulmonary / disseminated	4	0.1%	3	1.3%
	Kaposi's sarcoma	113	3.3%	5	2.2%
	Leishmaniasis visceral	5	0.1%	1	0.4%
	Microsporidiosis	5	0.1%	1	0.4%
	Mycobacterium avium/kansasii, extrapulmonary / disseminated	21	0.6%	5	2.2%
	Mycobacterium avium/kansasii, pulmonary	3	0.1%	0	0.0%
	Mycobacterium other / unspecified, extrapulmonary / disseminated	8	0.2%	3	1.3%
	Mycobacterium other / unspecified, pulmonary	5	0.1%	0	0.0%
	Non-Hodgkin`s lymphoma (NHL)	148	4.3%	9	4.0%
	Pneumocystis jirovecii extrapulmonary	1	0.0%	0	0.0%
	Pneumocystis jirovecii pneumonia	68	2.0%	13	5.8%
	Primary CNS lymphoma	5	0.1%	1	0.4%
	Progressive multifocal leukoencephalopathy	18	0.5%	5	2.2%
	Toxoplasmosis of the brain	19	0.6%	5	2.2%
	Tuberculosis, extrapulmonary / disseminated	45	1.3%	2	0.9%
	Tuberculosis, pulmonary	70	2.0%	3	1.3%
Subtotal		**1313**	**38.3%**	**131**	**58.2%**
Total		**3432**	**100.0%**	**225**	**100.0%**

Legend: *CDC=Centers for Disease Control and Prevention; CNS=Central Nervous System; MAI=mycobacterium avium intracellulare complex.*

	CD4 category									
	050–199		200–349		350–499		500–749		750+	
	n	%	n	%	n	%	n	%	n	%
	8	1.3%	1	0.1%	2	0.3%	1	0.1%	0	0.0%
	3	0.5%	1	0.1%	2	0.3%	11	1.5%	5	1.1%
	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
	7	1.1%	12	1.7%	16	2.4%	15	2.0%	5	1.1%
	0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
	14	2.2%	23	3.2%	28	4.2%	31	4.2%	12	2.7%
	3	0.5%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
	3	0.5%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
	7	1.1%	5	0.7%	2	0.3%	2	0.3%	0	0.0%
	0	0.0%	1	0.1%	0	0.0%	1	0.1%	1	0.2%
	2	0.3%	2	0.3%	0	0.0%	1	0.1%	0	0.0%
	2	0.3%	0	0.0%	2	0.3%	1	0.1%	0	0.0%
	41	6.4%	32	4.5%	30	4.5%	25	3.4%	11	2.4%
	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
	29	4.5%	10	1.4%	9	1.4%	5	0.7%	2	0.4%
	1	0.2%	2	0.3%	1	0.2%	0	0.0%	0	0.0%
	7	1.1%	3	0.4%	2	0.3%	1	0.1%	0	0.0%
	7	1.1%	4	0.6%	2	0.3%	1	0.1%	0	0.0%
	9	1.4%	5	0.7%	8	1.2%	11	1.5%	10	2.2%
	14	2.2%	21	2.9%	14	2.1%	10	1.4%	8	1.8%
	288	**45.1%**	**277**	**38.5%**	**262**	**39.7%**	**234**	**31.6%**	**121**	**26.9%**
	639	**100.0%**	**719**	**100.0%**	**660**	**100.0%**	**740**	**100.0%**	**449**	**100.0%**