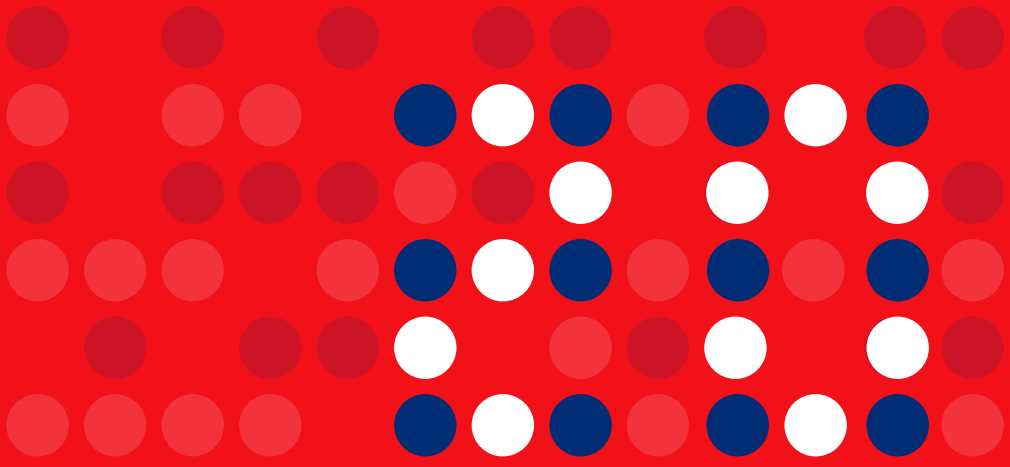
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2020



3. Morbidity and mortality

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Introduction

Since the introduction of cART, the life expectancy of HIV-1-positive individuals has markedly improved; in a subgroup of recently-diagnosed, effectively-treated individuals, it has been 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 such as renal and liver disease, diabetes mellitus, myocardial infarction, stroke, osteoporosis, and non-AIDS-defining malignancies, has increased among HIV-1-positive individuals during the cART era[3–8].

Various reports suggest that the risk of non-AIDS morbidity may be higher in HIV-positive individuals 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]. Of note, as is the case in HIV-negative individuals, traditional risk factors (e.g., tobacco use[19], alcohol abuse, and viral hepatitis co-infection[20]), also importantly 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 adult (18 years and older) HIV-1-positive individuals using updated Stichting HIV Monitoring (SHM) data: a total of 27,622 adult individuals ever registered by SHM – that breaks down as 27,407 adults and an additional 431 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 Centers for Disease Control (CDC) category C condition[23]. In contrast to what is usual in the United States, 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 2016-19. We standardised these estimates according to the age distribution of the population during the period 2016-19 (divided into the following age classes: 18-29, 30-39, 40-49, 50-59, 60-69, and ≥70 years) using the indirect method[24]. Indirect standardisation compares the incidence rates in the study and reference (period: 2016-19) 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 <200 cells/mm^3, known time spent with plasma HIV RNA >1000 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 27,622 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 8.0 (95% CI 6.8-9.5) per 1,000 PYFU in 2019 (*Figure 3.1A*). Despite this clear improvement over time, the mortality rate in HIV-1-positive adults remained well above the mortality of the general population in the Netherlands, which was 4.4 per 1,000 PYFU in 2019, when matched in terms of age and gender to our HIV-positive population. In the same group of 27,622 individuals, the incidence of AIDS decreased sharply from 121.0 (95% CI 108.5-134.6) in 1996 to 5.2 (95% CI 4.2-6.4) cases per 1,000 PYFU in 2019 (*Figure 3.1B*). The excess mortality can be partly ascribed to individuals who already had AIDS at the time of their HIV diagnosis, but much less so in recent years. When these individuals were excluded, the mortality rate decreased from 14.1 (95% CI 9.8-19.6) per 1,000 PYFU in 1996 to 7.6 (95% CI 6.3-9.1) per 1,000 PYFU in 2019. *Appendix Figure 3.1* shows the five-year survival curves after diagnosis of the first AIDS-defining condition.

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 high number of individuals who present late for care with immune deficiency that is already advanced. 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[a]. Table 3.1 shows the characteristics of adults who died of AIDS, compared to adults who died of non-AIDS causes in the period 2010 to 2019. 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 nearly 80% qualifying as a late presenter (CD4 count below 350 cells/mm^3). In addition, they had much lower nadir CD4 counts, and did not have controlled viremia in 60% of cases, of which 5.7% were 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 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 can also occur at higher 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 other men are overrepresented among those who died of non-AIDS causes, because these three groups have a higher average age compared to migrants, risk groups 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*.

a *Available on https://rivm.openrepository.com/handle/10029/622149, DOI: 10.21945/RIVM-2017-0158*

Table 3.1: Characteristics of adults who died of AIDS compared to adults who died of non-AIDS causes in the period 2010 to 2019. 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.

	Died of non-AIDS causes	Died of AIDS	p-value
Number of subjects	1120 (81.9%)	247 (18.1%)	
Age, years	57.3 (49.8-65.6)	52.6 (44.5-60.5)	<.001
Male gender	987 (88.1%)	204 (82.6%)	0.021
Dutch origin	798 (71.3%)	159 (64.4%)	0.038
MSM	616 (55.0%)	109 (44.1%)	0.002
Heterosexuals	281 (25.1%)	80 (32.4%)	0.021
Other risk groups	223 (19.9%)	58 (23.5%)	0.223
Years since HIV diagnosis	13 (6.8-19.2)	5.49 (0.51-13.4)	<.001
Years since cART was started	10.2 (4.74-15.7)	1.55 (0.26-11.4)	<.001
CD4 at HIV diagnosis	280 (100-500)	100 (30-310)	<.001
Late presenter (CD4<350 at entry in care)	646 (57.8%)	189 (78.4%)	<.001
Very late presenter (CD4<200)	421 (37.6%)	158 (64.0%)	<.001
CD4 nadir	125 (50-240)	45 (10-100)	<.001
Last CD4 measured before death	440 (260-640)	121 (40-270)	<.001
Not undetectable at date of death	212 (19.1%)	138 (59.7%)	<.001
Not on cART at date of death	29 (2.6%)	14 (5.7%)	0.024

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 3.1A-B: (A) Annual mortality and (B) incidence of AIDS in 27,622 HIV-1-positive individuals in the Netherlands after HIV diagnosis 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 gender-matched individuals from the general population in the Netherlands.

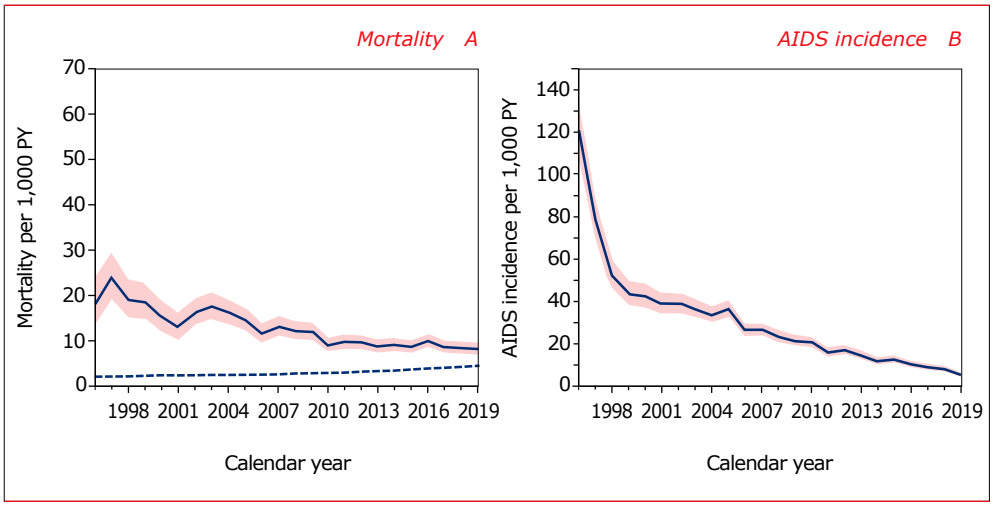
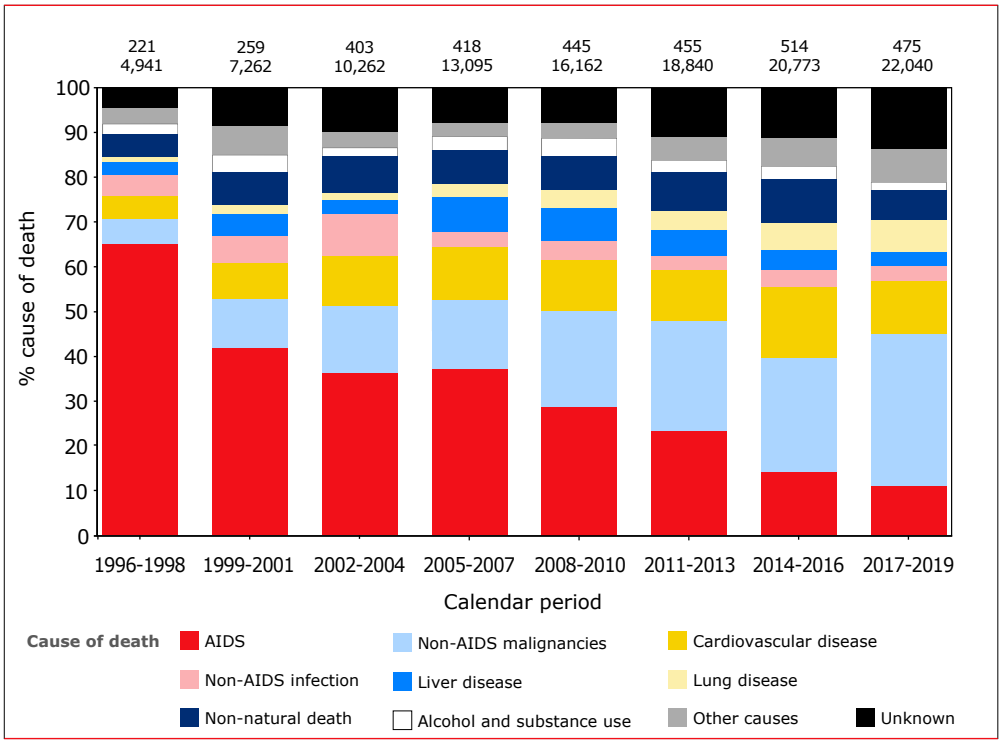


Figure 3.2: Relative changes in causes of death in different calendar periods since the introduction of combination antiretroviral therapy (cART) in the Netherlands. The numbers at the top of each bar represent the total number of deaths and the total number of individuals that were at risk during that calendar period. Mortality attributed to 'alcohol use' consisted of 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 of starting 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 HBV or 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 underestimated.

In contrast to previous SHM Monitoring Reports, 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 with HIV in the Netherlands in the period 2011 to 2018 was stable at around ten recorded cases per calendar year; the lower number of three suicides recorded in 2019, appears to be an outlier and might be caused by late reporting of causes of death. For patients with a serious somatic condition who were euthanized 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 2019, a total of 130 cases of euthanasia were recorded; 35% of cases occurred in patients who died of AIDS, 39% in patients who died of non-AIDS-defining malignancies, and the remaining 26% occurred in patients who died of other somatic 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

The incidence of the first occurrence of any AIDS-defining event after entering care was 21.4 events per 1,000 PYFU of follow up. *Appendix Table 3.4* gives an overview of the AIDS events occurring between 1996 and 2019. The most common AIDS events between 2016 and 2019 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 the hepatitis C virus.

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 2019, 23,882 individuals contributed a total of 201.2 thousand PYFU, during which 3,170 CDC-B and/or AIDS-defining events were diagnosed. This resulted in an incidence rate of 15.8 events per 1,000 PYFU (1,924 CDC-B events, 9.6 events/1,000 PYFU; 1,246 CDC-C/AIDS events, 6.2 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 11.4 and 5.7 AIDS-defining illnesses/1000 PYFU, respectively. The incidence rates of AIDS-defining illnesses in the CD4 strata of 500-749 and over 750 cells/mm^3 were 3.1 (2.7-3.6) and 1.9 (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 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 in individuals on cART while having an undetectable viral load between 2000 and 2019.

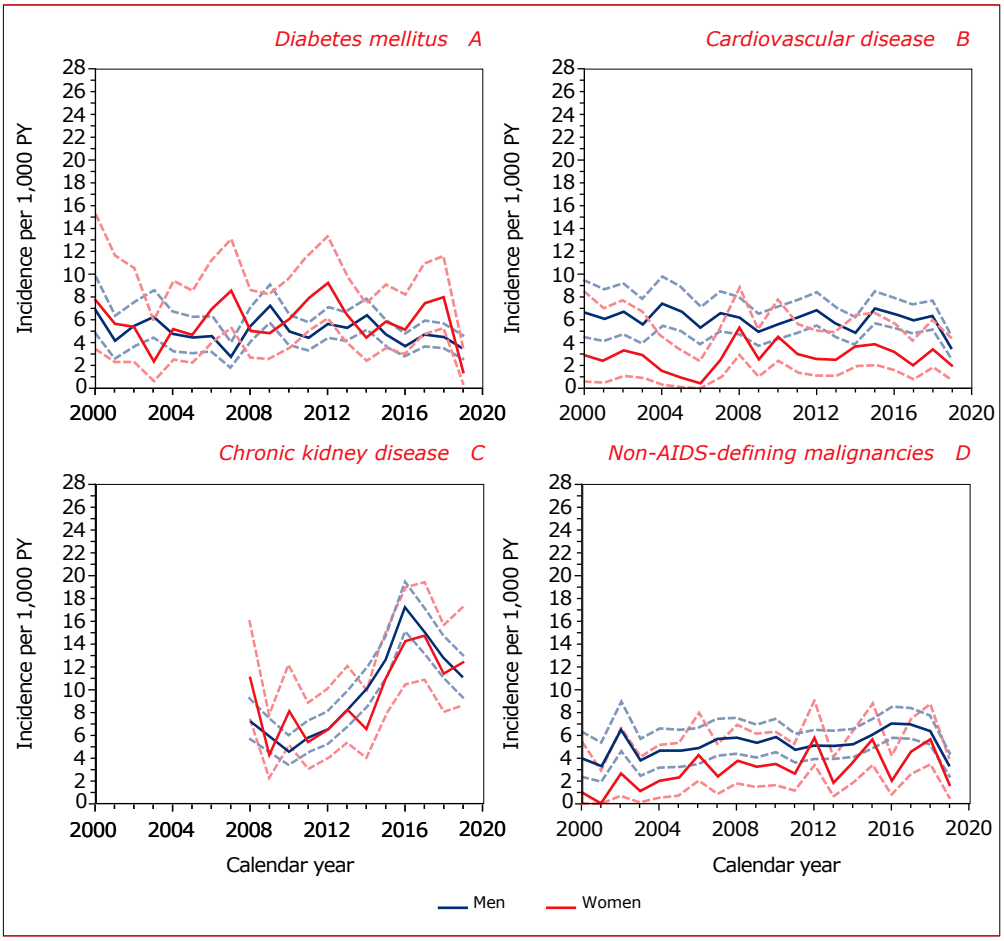
CD4 category (cells/mm³)	CDC events (n)	CDC B events (n)	CDC C events (n)	PYFU follow-up (x1000)	Incidence rate CDC events (/1000 PY) (95%CI)	Incidence rate CDC-B events (/1000 PY) (95%CI)	Incidence rate CDC-C events (/1000 PY) (95%CI)
0-50	244	100	144	0.5	513 (451-581)	210 (171-256)	303 (255-356)
50-199	569	317	252	7.9	72.1 (66.3-78.2)	40.1 (35.9-44.8)	31.9 (28.1-36.1)
200-349	697	415	282	24.7	28.2 (26.1-30.4)	16.8 (15.2-18.5)	11.4 (10.1-12.8)
350-499	607	367	240	42.4	14.3 (13.2-15.5)	8.66 (7.79-9.59)	5.66 (4.97-6.43)
500-749	667	444	223	71.1	9.38 (8.68-10.1)	6.25 (5.68-6.86)	3.14 (2.74-3.58)
750+	386	281	105	54.7	7.06 (6.37-7.80)	5.14 (4.56-5.78)	1.92 (1.57-2.33)
Total	**3170**	**1924**	**1246**	**201.2**	**15.8 (15.2-16.3)**	**9.56 (9.14-10.0)**	**6.19 (5.85-6.55)**

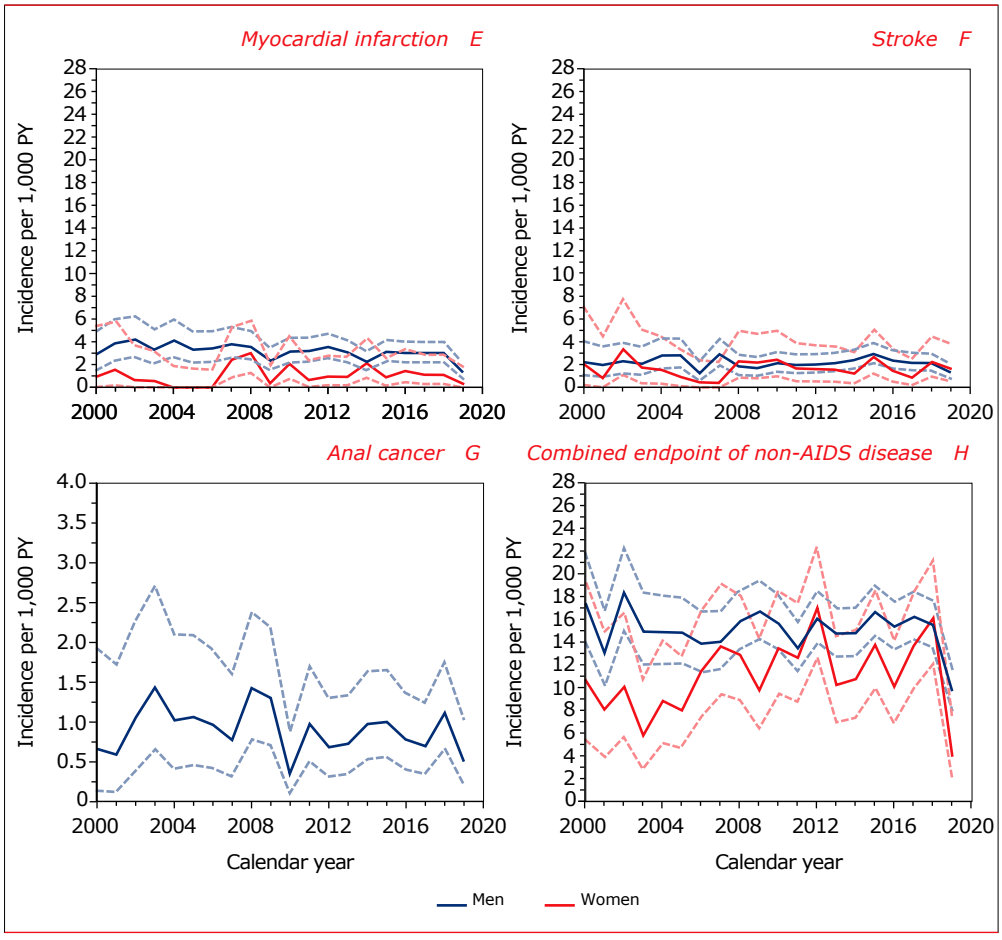
***Legend:** CDC=Centers for Disease Control and Prevention Classification System for HIV Infection; CDC-B=moderately symptomatic HIV disease; CDC-C=AIDS-defining events; cART=combination antiretroviral therapy; PYFU=person years of follow up.*

Non-AIDS-defining events

Of the 27,622 HIV-1-positive adults ever registered with SHM, 27,064 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 3.3A-H: *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. Legend: PYFU=person years of follow up.*





Diabetes mellitus

Of the 27,064 individuals aged 18 years or older and in follow up in, or after January 2000, a total of 1,346 (1,039 men and 307 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.3A*) and, in 2019, was 3.5 (95% CI 2.6-4.6) per 1,000 PYFU in men and 1.4 (95% CI 0.4-3.6) per 1,000 PYFU in women. In men, the age-standardised incidence ratio declined over time and was significantly lower in 2016-19 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 2016-19 (*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 NRTIs prior to starting cART; and a prior AIDS diagnosis (*Appendix Table 3.6*). Moreover, the risk of new-onset diabetes in the periods 2000-10 and 2011-15 was significantly higher than in the period 2016-19. 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 during 2000–10, 2011–15 and 2016–19 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)	1.69 (1.53–1.84)	5.7 (4.8–6.8)	1.10 (0.91–1.29)
2011–2015	5.3 (4.8–5.9)	1.44 (1.29–1.59)	6.7 (5.5–8.1)	1.23 (0.99–1.47)
2016–2019	4.2 (3.7–4.7)	1 (reference)	5.7 (4.5–7.2)	1 (reference)

**Standardised according to the observed age distribution between 2016–19.*

Legend: *CI=confidence intervals; PYFU=person years follow up.*

Cardiovascular disease

From January 2000 onwards, 1,399 individuals (1,251 men and 148 women) had a fatal or non-fatal cardiovascular event. Of these, 683 had a myocardial infarction, 514 a stroke, 103 a coronary artery bypass graft, 524 a coronary angioplasty or stenting, and 11 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 <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. Cardiovascular risk was also higher during 2000-10 and 2011-15 than during 2016-19, 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 1.64 to 1.49, p<0.001. Having an eGFR below 90 ml/min was independently associated with a higher risk of CVD; at 60-90 ml/min, the IRR was 1.11 (95% CI 0.96-1.28), p=0.17; at 30-60 ml/min the IRR was 1.74 (1.40-2.17), p<0.001; at 15-30 ml/min, the IRR was 4.66 (3.06-7.09), p<0.001; and at 0-15 ml/min the IRR was 4.45 (2.48-7.99), p<0.001.

From January 2000 onwards, 189 men and 15 women experienced a fatal or non-fatal secondary cardiovascular event (123 had a myocardial infarction, 89 had a stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2019 in men and women with a prior cardiovascular event was 27.9 (95% CI 24.1-32.2) and 16.4 (95% CI 9.2-27.0), 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: 31.2 events per 1,000 PYFU; SIR: 1.33, 95% CI 1.04-1.63), but not during 2011-15 (crude rate: 25.0 events per 1,000 PYFU; SIR: 1.05, 95% CI 0.79-1.31) compared with the reference period 2016-19 (crude rate: 23.8 events per 1,000 PYFU).

Table 3.4: *Crude incidence of cardiovascular disease per 1,000 person years of follow up between 2000–10, 2011–15, and 2016–19 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	6.1 (5.6–6.6)	1.53 (1.39–1.66)	2.7 (2.1–3.5)	1.52 (1.14–1.90)
2011–2015	6.1 (5.5–6.7)	1.24 (1.12–1.37)	3.1 (2.3–4.1)	1.36 (0.98–1.73)
2016–2019	5.6 (5.1–6.3)	1 (reference)	2.7 (1.9–3.7)	1 (reference)

**Standardised according to the observed age distribution between 2016–2019.*

Legend: *CI=confidence intervals; PYFU=person years of follow up.*

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 2019, the proportion of men with available BMI data who were overweight (25-30 kg/m^2), or obese (class I: 30-35 and class II: ≥35 kg/m^2), was 34%, 8% and 2%, respectively. In women, these respective proportions were 31%, 18% and 11%.

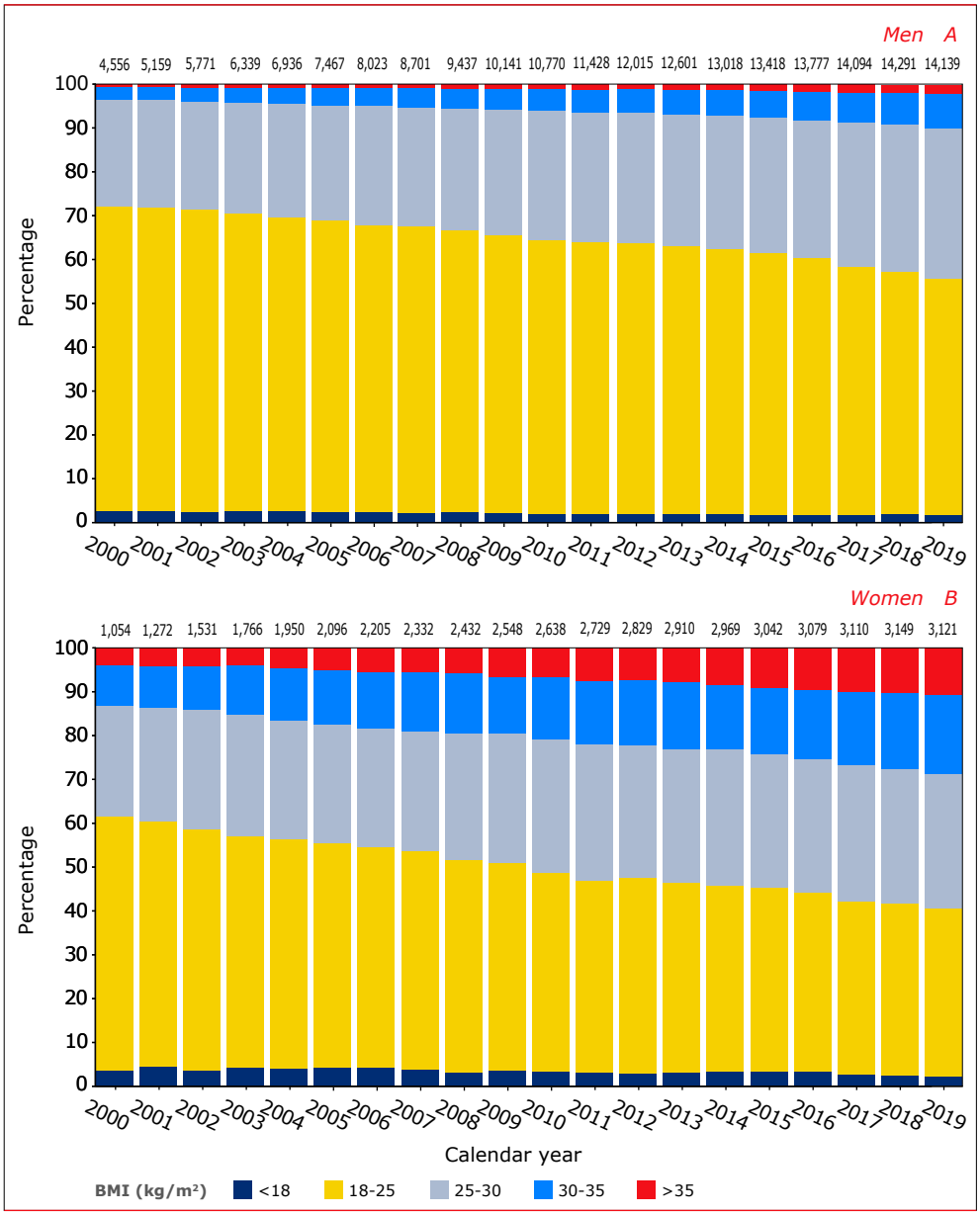
Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the HIV-positive population. This analysis revealed that the increase

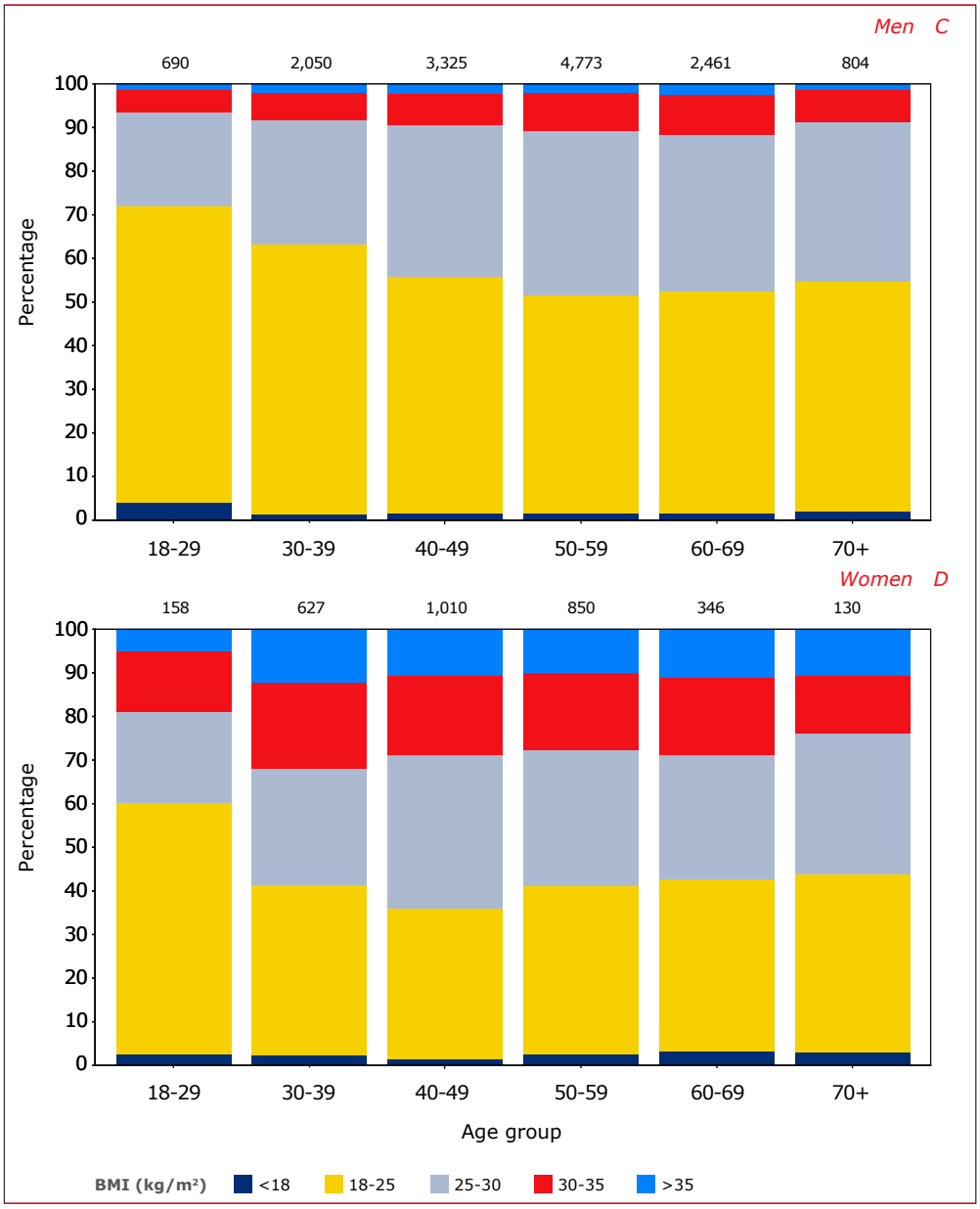
was at least partially driven by changes over time in population demographic characteristics (age, region of origin, transmission risk group) and time since first start of cART, and that this effect was more marked in men than in women.

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 2019 for men and women. Whereas in adult men of all age groups, the proportion classified as obese (10%) was substantially lower than the proportion found in the general Dutch male population (11.3%), in women of all age groups there was more obesity (28%) than in the general Dutch female population (14.0%)[25]. There were substantial differences between native Dutch, Western migrants and non-Western migrants: among males, 9.0% of Dutch, 10.7% of Western migrants and 12.1% of non-Western migrants were obese, whereas in females, those figures were 20.6%, 16.3%, and 34.2%, respectively. Being obese (a BMI over 30) was independently associated with an increased risk of diabetes (IRR 4.82, 95% CI 4.08-5.69, p<0.001) and CKD (IRR 1.19, 95% CI 1.02-1.40, p=0.032), but that was not the case with CVD or non-AIDS-defining malignancies (*Appendix Table 3.7*).

Figure 3.5A shows that, in 2019, 48% of those treated with antihypertensives still had grade 1 hypertension or higher. The figures above the bars show that, over time, an increasing number of individuals used antihypertensives. In 2019, 25% (3,890) of individuals not using antihypertensives had grade 1-3 hypertension (*Figure 3.5B*). For 3,588 of these 3,890 individuals, a five-year cardiovascular disease (CVD) risk could be calculated with the recalibrated D:A:D study algorithm[26]. Of the 3,588 individuals, 5.8% 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[27]. *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%) five-year risk were 12% and 5%, respectively, which steadily increased to 20% and 12%, respectively, in 2019. The increase in the percentage of individuals at high or very high risk likely reflects the ageing of the population being studied.

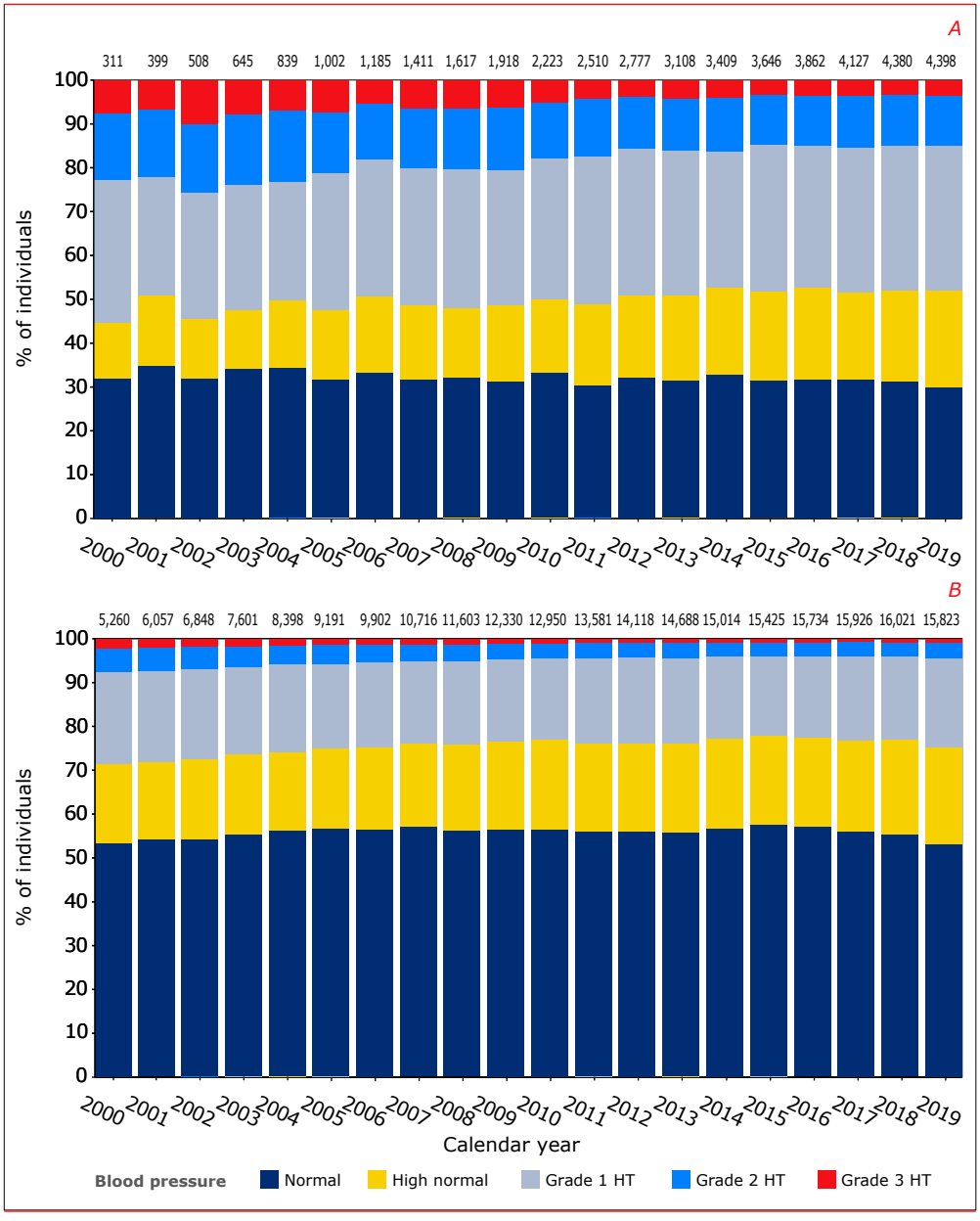
Figure 3.4A-D: Distribution of the body mass index (BMI) at the end of each calendar year in (A) men, and (B) women, as a percentage of the total number of men and women with a known BMI in each year, and distribution of the BMI over the age groups for (C) men, and (D) women, in 2019. For each individual, 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).





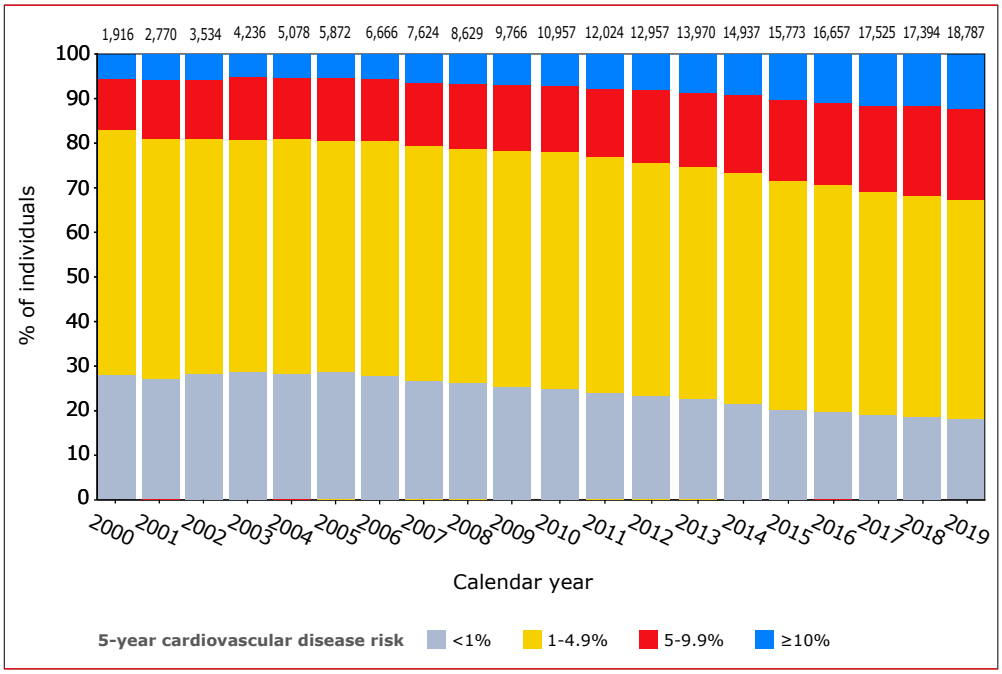
Legend: BMI=body mass index.

Figure 3.5A-B: 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[28]). 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[26]. 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.



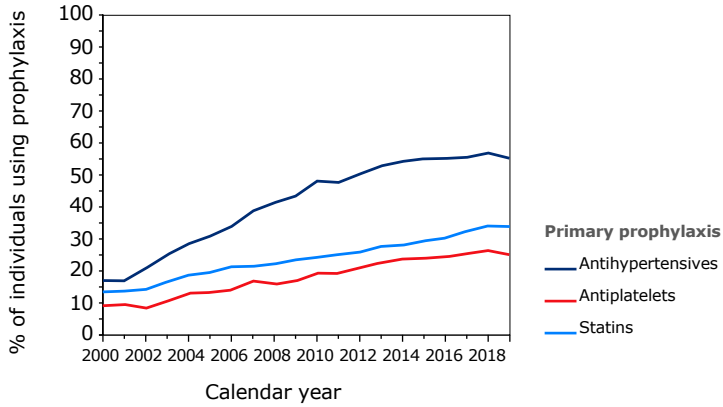
Use of primary or secondary preventive therapy for myocardial infarction or stroke

Primary prevention

According to EACS guidelines, statin therapy should be offered to individuals with type 2 diabetes or a ten-year CVD risk ≥10%. They also recommend that angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, diuretics, and antihypertensives (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[29]. 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[b] *Figure 3.7* 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 five years.

Figure 3.7: *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.*



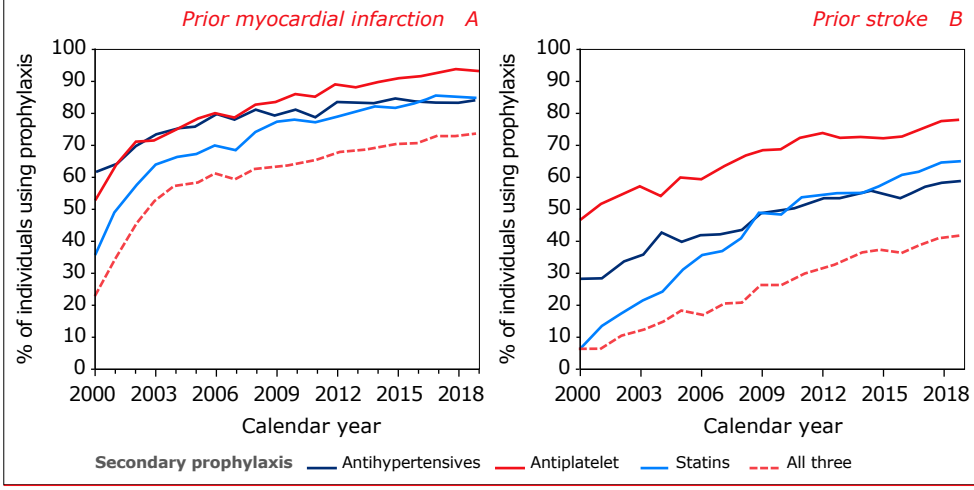
Secondary prophylaxis for myocardial infarction or stroke

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[30,31]. *Figure 3.8A* shows that the percentages of individuals using statins, acetylsalicylic acid/clopidogrel, or antihypertensives after a myocardial infarction increased between 2000 and 2019: in 2019, 85% of individuals with a prior myocardial infarction used statins, 84% used anti-hypertensives, and 93% used acetylsalicylic acid/clopidogrel. Although the use of

b *Richtlijn Cardiovasculair Risicomanagement (CVRM) 2018, https://www.nhg.org/sites/default/files/content/nhg_org/uploads/multidisciplinaire_richtlijn_cardiovaculair_risicomanagement.pdf*

statins and antihypertensives after an ischaemic stroke also increased over time, in 2019 these medications were used less frequently after a stroke than after a myocardial infarction (65% for statins, 78% for acetylsalicylic acid/clopidogrel, and 59% for antihypertensives) (*Figure 3.8B*).

Figure 3.8A-B: *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[32]. 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 HIV-positive individuals[32,33]. 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, normal kidney function; 60-89, mildly reduced; 30-59, moderately reduced; 15-29, severely reduced; and <15, very severely reduced kidney function) is shown in *Figures 3.9A and B* for men and women. The percentage of men with normal kidney function decreased over time from 75% in 2007, to 44% in 2019, 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 >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 <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 7.2 cases per 1,000 PYFU in the period 2008-14 to 12.7 in 2015-19. In women, the incidence rose from 7.3 to 13.1 cases per 1,000 PYFU during the same periods (*Table 3.5*). The standardised incidence ratio in men, but not in women, increased significantly over time (*Table 3.5*).

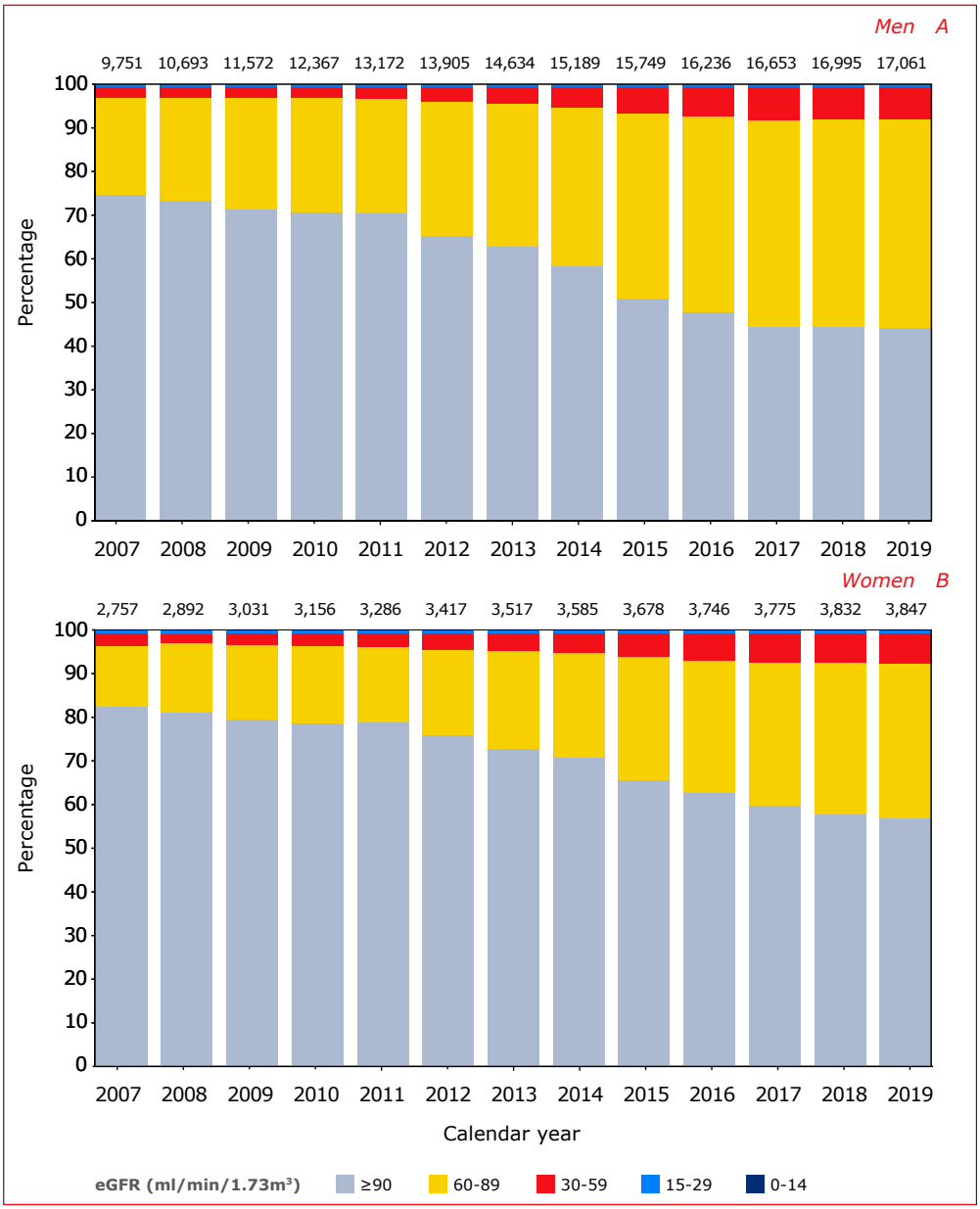
Risk factors for CKD included: female gender; Dutch origin; low current CD4 cell count (<200 cells/mm^3); a prior AIDS diagnosis; belonging to the HIV transmission risk group of people who inject drugs; older age group; lower body mass index; hypertension; diabetes mellitus; cardiovascular disease; pre-treatment with monotherapy and dual therapy with nucleoside analogues before the start of cART; and chronic HBV and HCV co-infection (*Appendix Table 3.6*). When current use of cobicistat, rilpivirine, dolutegravir, and bictegravir were added to the model, the increased risk of CKD in the calendar period 2016-19 completely disappeared in comparison to 2008-10 and 2011-15. This 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 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 (> 12 months) TDF-containing regimen to a TAF-containing regimen. We compared the serum creatinine levels measured within 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 325 subjects fulfilled the above criteria and switched from TDF to TAF because of renal toxicity / elevated serum creatinine. Another 2,637 subjects also fulfilled the above criteria but switched from TDF to TAF for other reasons. The 325 subjects who switched because of renal toxicity, had a median serum creatinine level of 116 (IQR 106-125) micromol/L prior to the switch, and showed a median change of -6 (IQR 0 to -15) micromol/L ≥6 months after the switch. The 2,637 subjects who switched because of other reasons had a median serum creatinine level of 88 (IQR 77-100) micromol/L prior to the switch, and showed a median change of -1 (IQR +5 to -7) micromol/L ≥6 months after the switch.

Using the same approach as for the switch from TDF to TAF, we also looked at changes in serum creatinine in subjects who initiated dolutegravir, bictegravir, rilpivirine, ritonavir or cobicistat, without a concomitant switch (start or stop) of any of the other OCT2 / MATE1 inhibitors, nor of TDF or TAF. In 848 subjects who initiated dolutegravir without concomitant changes in any other OCT2 / MATE1 inhibitor, TDF or TAF, the pre-switch median serum creatinine level was 81 (IQR 71-94) micromol /L and the change in serum creatinine ≥6 months after the switch was +11 (IQR +5 to +18) micromol/L. In 664 subjects switching to rilpivirine with a median baseline creatinine level of 81 (IQR 71-91) micromol/L, the median change was +9 (IQR +3 to +15) micromol/L. In 859 subjects switching to ritonavir (100mg once daily) with a median baseline creatinine level of 75 (IQR 63-85) micromol/L, the median change was +3 (IQR -4 to +10) micromol/L. In 292 subjects switching to cobicistat with a median baseline creatinine level of 82 (IQR 72-92) micromol/L, the median change was +9 (IQR +3 to +18) micromol/L. Not enough subjects switched to bictegravir without a concomitant switch (start or stop) of any of the other OCT2 / MATE1 inhibitors, nor of TDF or TAF, to allow for a reliable estimation of the effect of this switch on serum creatinine levels.

Figure 3.9A-B: 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.



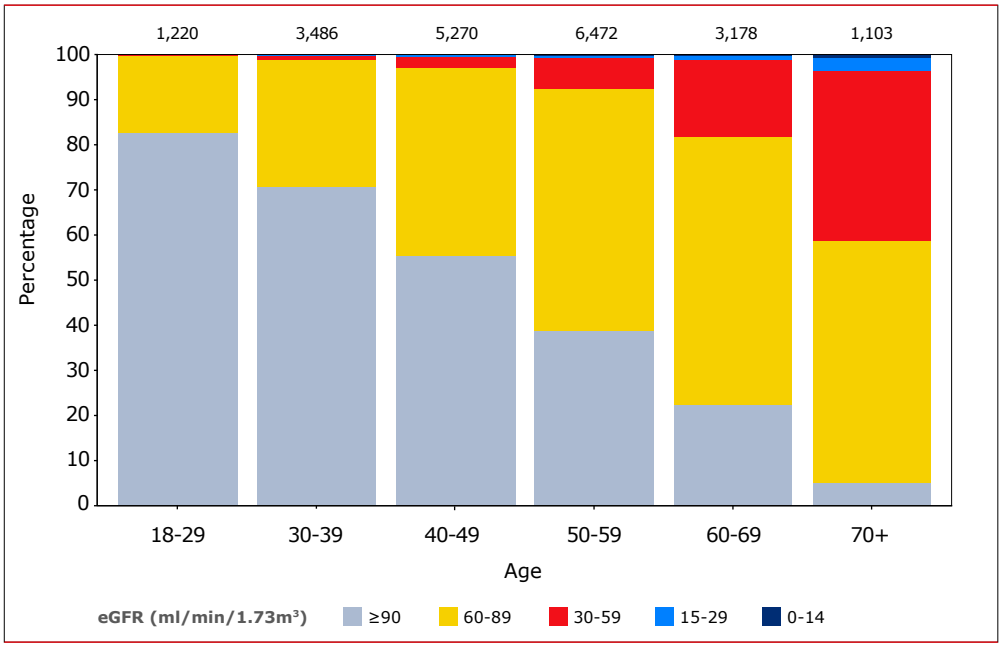
Legend: eGFR=estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60-89 ml/min/1.73m²: mildly reduced; 30-59 ml/min/1.73m²: moderately reduced; 15-29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.

Table 3.5: Crude chronic kidney disease incidence per 1,000 person years of follow up between 2008-14, and between 2015-19, 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	7.2 (6.5-8.1)	0.70 (0.62-0.77)	7.3 (5.8-9.0)	0.79 (0.62-0.97)
2015-2019	12.7 (11.7-13.7)	1 (reference)	13.1 (11.0-15.5)	1 (reference)

**Standardised according to the observed age distribution between 2015-2019.*
***Legend:** CI=confidence interval; PYFU=person years of follow up.*

Figure 3.10: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2019 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 2019, 1,707 diagnoses of non-AIDS-defining malignancy in 1,585 unique individuals were recorded in SHM's database. An additional 696 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 (17%); haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 15%); intestinal cancer (excluding liver cancer, 13%); invasive anal cancer (not AIN, 12%); prostate cancer (9%); and head and neck cancers (8%). *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 2016-19, 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 2016-19, than in 2000-10, and to a lesser extent 2011-15 (*Table 3.7*).

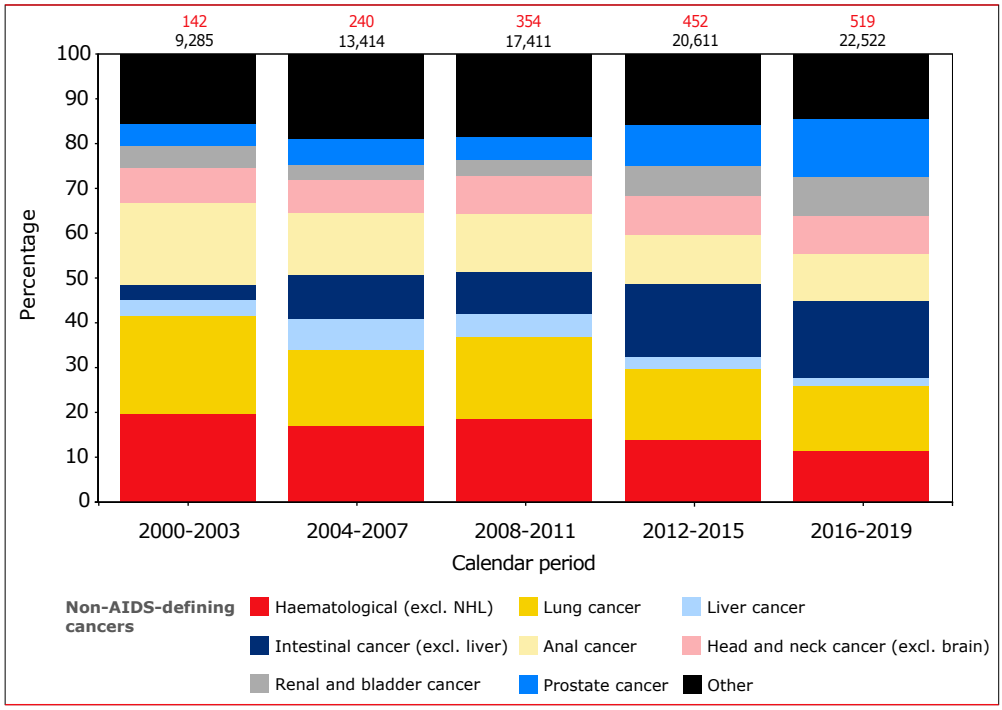
Demographic and clinical factors independently associated with an increased risk of a first non-AIDS-defining malignancy were: older age group; acquiring HIV-1 through injecting drugs or contact with blood or blood products; lower current CD4 cell count (CD4 below 350 cells/mm^3); low body mass index; prior AIDS; chronic HBV co-infection; and current or past smoking (*Appendix Table 3.6*). Furthermore, people who had not yet started cART, or 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] 1.25 (95% CI 1.00-1.57) and 1.20 (1.03-1.41) respectively). 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 0.54, 95% CI 0.33-0.86) 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 2019, 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%, compared with 75.7% for CVD, 81.5% for DM, and 86.0% for CKD (*Appendix Figure 3.1*). In the same period, the five-year survival rate of adults newly-entering care in one of the Dutch HIV treatment centres was 95.6%, and 82.2% 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

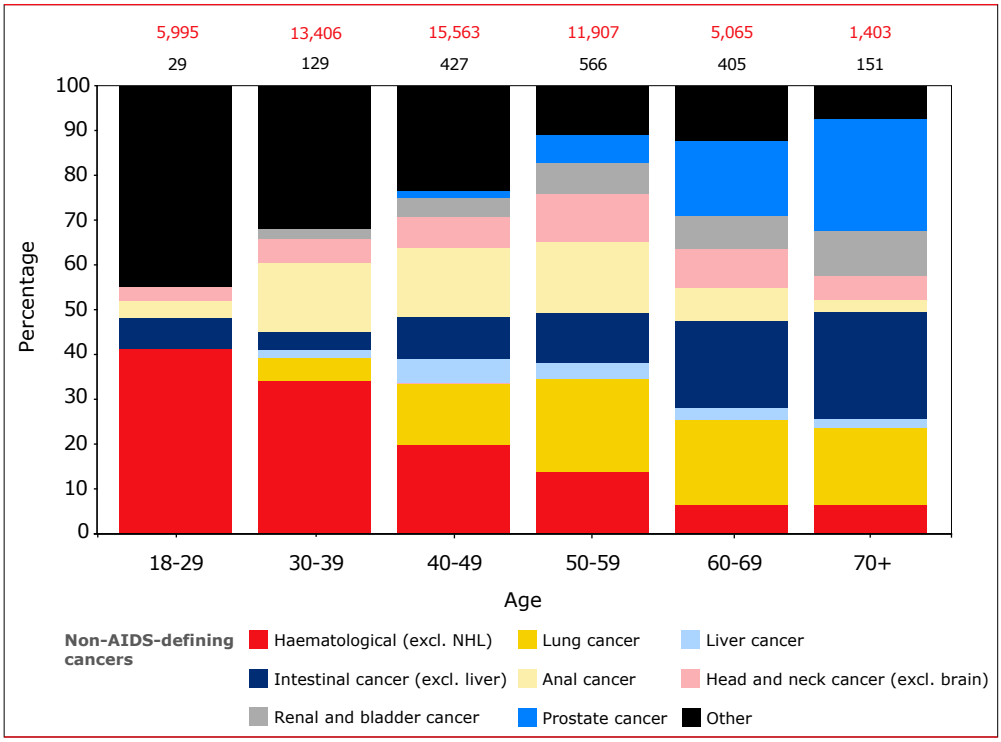
In total, 201 HIV-positive men and seven HIV-positive women were diagnosed with anal cancer. Among HIV-positive men, the incidence of anal cancer fluctuated between 0.5 and 1.4 cases per 1,000 PYFU between 2000 and 2019 (*Figure 3.3G*). A 2015 study exploring the incidence of anal cancer among HIV-1-positive individuals in the Netherlands showed a significantly higher incidence of anal cancer in men who have sex with men (MSM), than in heterosexual men[34]. 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=22) to analyse.

Figure 3.11: Relative changes in non-AIDS-defining malignancies between 2000 and 2019 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 during that calendar period.



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 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 2019.



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

Table 3.6: Most common non-AIDS-defining malignancies diagnosed between 2000-19, 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	284	16.6	15.1
Haematological cancer (excluding non-Hodgkin's lymphoma)	258	15.1	65.1
Anal cancer	226	13.2	33.0
Intestinal cancer (excluding liver)	208	12.2	63.4
Head and neck cancer (excluding brain)	149	8.7	80.0
Prostate cancer	143	8.4	58.3
Other cancers	103	6.0	67.3
Renal and bladder cancer	96	5.6	48.9
Malignant melanoma	73	4.3	73.0
Liver cancer	59	3.5	14.2
Breast cancer	44	2.6	81.7
Testicular cancer	33	1.9	86.2
Gynaecological cancer (excluding cervical)	24	1.4	64.6
Central nervous system (CNS) cancer	7	0.4	57.1

Table 3.7: Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up between 2000-10, 2011-15, and 2016-19, 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 (6.1-7.1)	1.36 (1.24-1.47)	3.1 (2.5-3.9)	1.28 (0.98-1.57)
2011-2015	6.6 (6.0-7.2)	1.07 (0.97-1.17)	4.3 (3.3-5.4)	1.18 (0.90-1.46)
2016-2019	7.3 (6.6-8.0)	1 (reference)	4.4 (3.4-5.7)	1 (reference)

**Standardised according to the observed age distribution between 2011-2019.*

***Legend:** CI=confidence intervals; PYFU=person years of follow up*

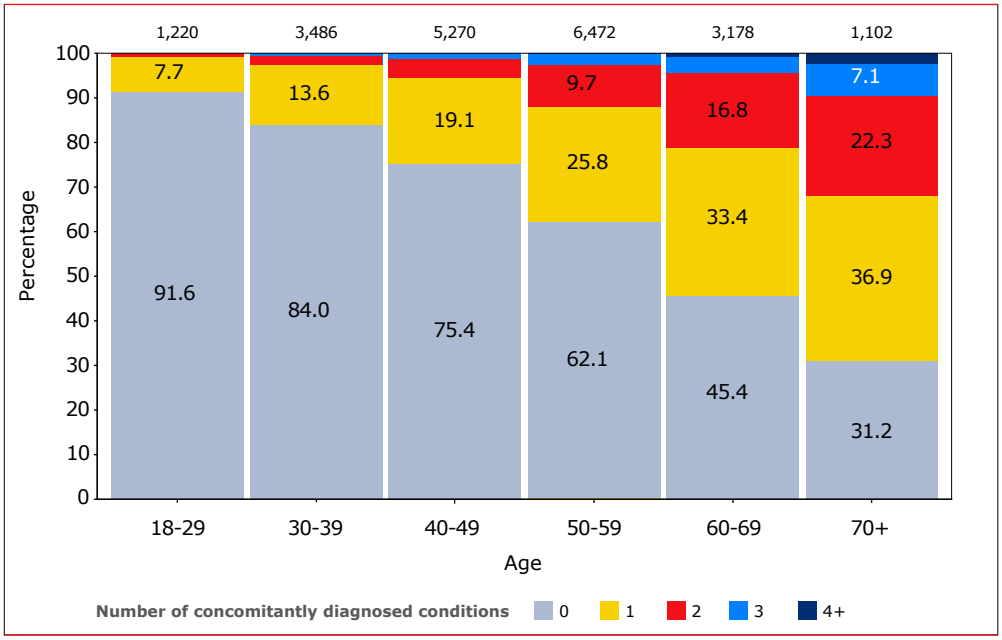
Multimorbidity

We have also 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 ≥160 mmHg and/or diastolic pressure ≥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 2019. 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 2.17, 95% CI 2.08-2.26, $p<0.001$, per additional comorbidity diagnosed).

Figure 3.13: Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2019. 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[c]) of the comedications. Note that coformulated combinations, such as cotrimoxazole, have a single ATC code and therefore increase the comedication count by one.

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

In 2019, 23.5% of adults in active follow up had no recorded comedication use, while 32.4%, 15.7%, 9.6%, and 6.2% used one, two, three or four comedications, respectively. A further 12.7% used five or more non-antiretroviral comedications in addition to their cART regimen, which qualifies as polypharmacy. The prevalence of polypharmacy among adults has increased over calendar time (*Figure 3.14*): in 2000, just 3.0% 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 2007-19, polypharmacy was also associated with an increased risk of death (RR 2.44, 95% CI 2.17-2.74, $p<0.001$) independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities (i.e., multimorbidity). All comedications used by at least 250 adult patients in care in 2019 are listed in *Table 3.8*.

Table 3.8: Use of comedications in 2019.

Comedication use in 2019	n	%
ATC group		
Vitamins	4576	11.1
Lipid modifying agents	3823	9.3
Drugs for acid-related disorders	3281	8.0
Agents acting on the renin-angiotensin system	2926	7.1
Antithrombotic agents	2446	6.0
Psychoanaleptics	2021	4.9
Mineral supplements	1932	4.7
Drugs used in diabetes	1698	4.1
Beta blocking agents	1527	3.7
Urological drugs	1481	3.6
Psycholeptics drugs	1295	3.2
Calcium channel blockers	1258	3.1
Antibacterial drugs	1087	2.6
Sex hormones and modulators of the genital system	996	2.4
Drugs for obstructive airway diseases	985	2.4
Diuretic drugs	976	2.4
Antianaemic drugs	933	2.3
Antiepileptic drugs	751	1.8
Analgesic drugs	736	1.8
Antiviral drugs	670	1.6
Corticosteroids systemic	553	1.3
Cardiac therapy	532	1.3
Nasal preparations	482	1.2
Antimycotic drugs	431	1.0
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	384	0.9
Drugs affecting bone structure and mineralisation	342	0.8
Thyroid therapy	313	0.8

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.

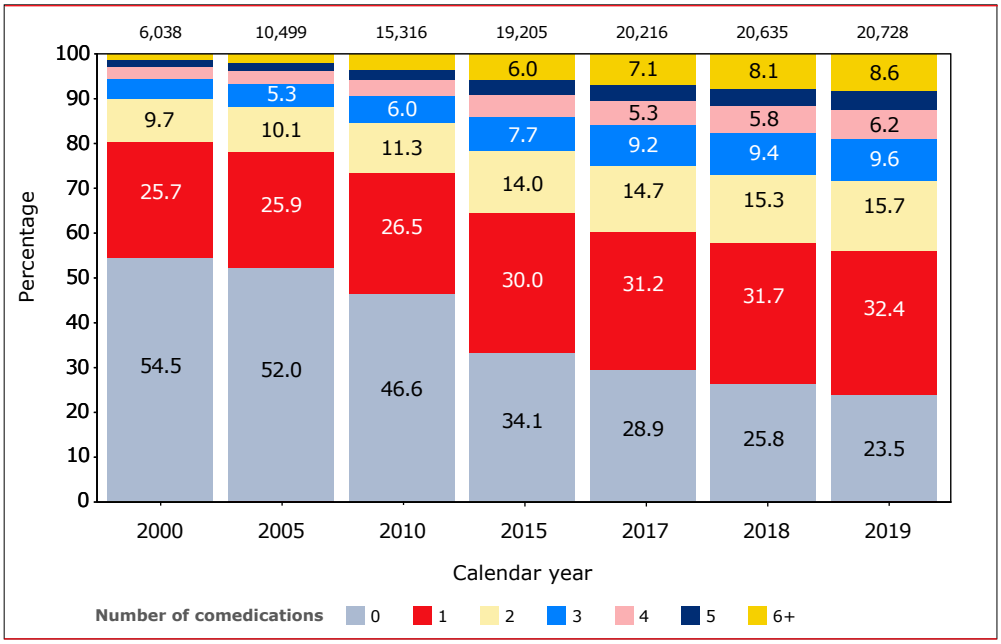
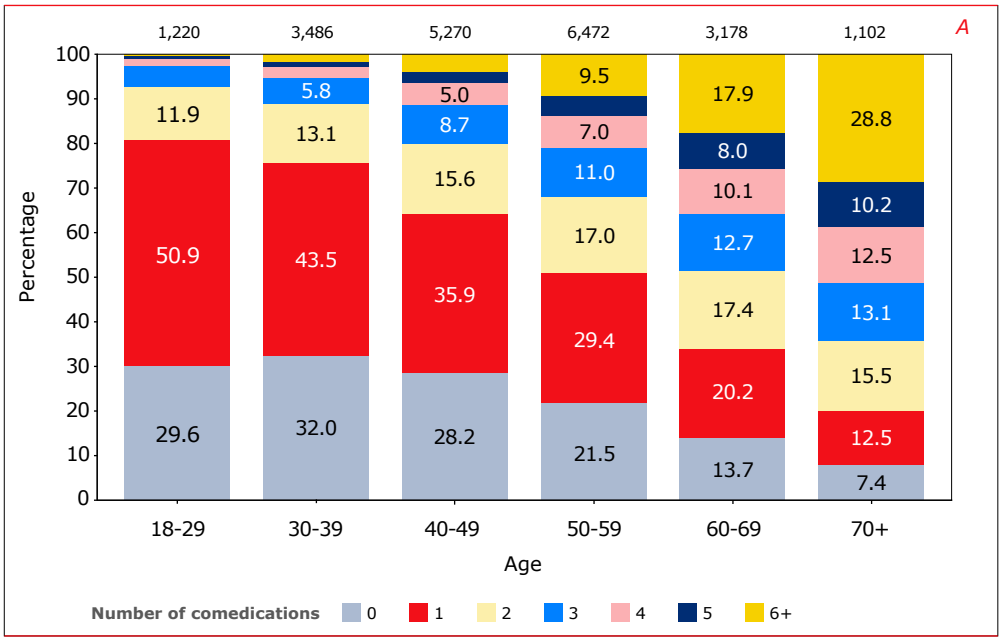


Figure 3.15A-B: Number of comedications used by (A) age group, and (B) gender. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



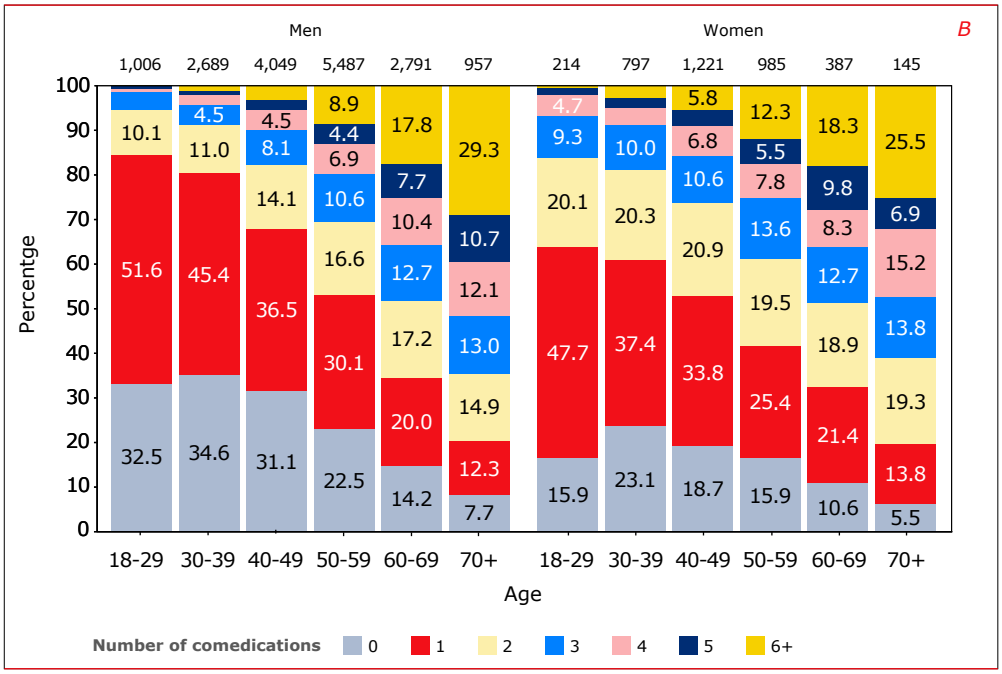
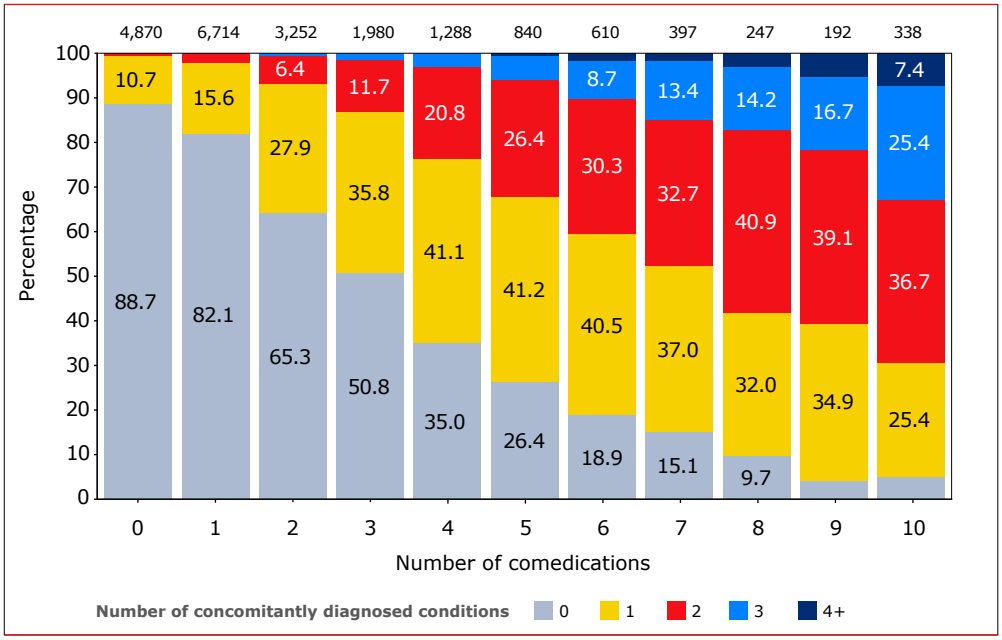


Figure 3.16: Number of comedications used in relation to the number of prevalent comorbidities. The numbers at the top of each bar represent the number of individuals contributing data to that category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per 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, consistent with reductions reported in studies from Spain[35], Denmark[36], several other European countries[37], and the USA[38]. The limited, but decreasing, number of individuals who still die of AIDS each year, are mainly those who present late for care with already advanced immunodeficiency. Nonetheless, overall, the five-year survival rate after a first AIDS-defining condition was 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, mortality rates among people living with HIV remain higher than in the

general population, although they do approach, or may even drop below, general population rates in individuals who achieve CD4 counts above 500 cells/mm^3 on treatment[39,40].

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 both diseases declined over time in men. This decline may suggest improved awareness, prevention (including switching from drugs associated with an increased risk of diabetes mellitus[41] and myocardial infarction[42,43] to those that, to date, have not been associated with such risks), 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 because an increasing proportion of individuals have been using cART long enough to have reached high CD4 cell counts). The observation that the age-standardised incidence ratios do not decline as much in women remains unexplained and needs further study. 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[41,44,45]. Several of these risk factors have been reported to be more prevalent among people living with HIV[19].

Cardiovascular risk factors

Despite the increasing age of the HIV-positive population, the proportion at high, or very high cardiovascular risk increased only slightly over the period 2000-19. This suggests 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[46] (*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 clinical significance of the increase in BMI over time, especially in women, requires further study. Recent results have suggested that weight gain after starting cART is associated with lower mortality for normal-weight individuals, but have found no clear benefit for overweight or obese individuals[47]. 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[48]. 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 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 for CKD, as were individuals with advanced immunodeficiency. In addition, other studies have also reported hepatitis B and C virus co-infection[49,50], and the use of tenofovir disoproxil fumarate, atazanavir/ritonavir, and lopinavir/ritonavir, to be additional independent predictors of chronic renal impairment[51]. Moreover, renal impairment in the HIV-positive population is associated with an increased risk of cardiovascular disease[52]. 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, anal, and head and neck cancer, as well as Hodgkin's lymphoma. The crude incidence of NADM in the Netherlands has remained stable over time, and we also observed a decline in age-standardised incidence of NADM in men. In addition, our analyses showed that individuals diagnosed with NADM were more likely to be older. This is in line with data from other cohorts, including the Swiss HIV cohort, that have also reported an increased incidence of NADM with increasing age[53–56]. 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[57]. 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 independently associated with increased risk of mortality (RR 2.17, 95% CI 2.08-2.26, p<0.001, per additional comorbidity diagnosed).

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 12.7% of adults in active follow up in 2019. 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 2007-19, polypharmacy was also associated with an increased risk of death (RR 2.44, 95% CI 2.17-2.74, p<0.001), 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 in order 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[58–60]. 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 people newly-entering care with an AIDS diagnosis, underlines the importance of primary prevention, early diagnosis and aggressive pursuit of secondary prevention and treatment of non-AIDS comorbidities in the HIV-positive population. Studies such as the ongoing Comorbidity and Aging with HIV (AGE_nIV) 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[9,61].

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 multimorbidity, 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 concerning 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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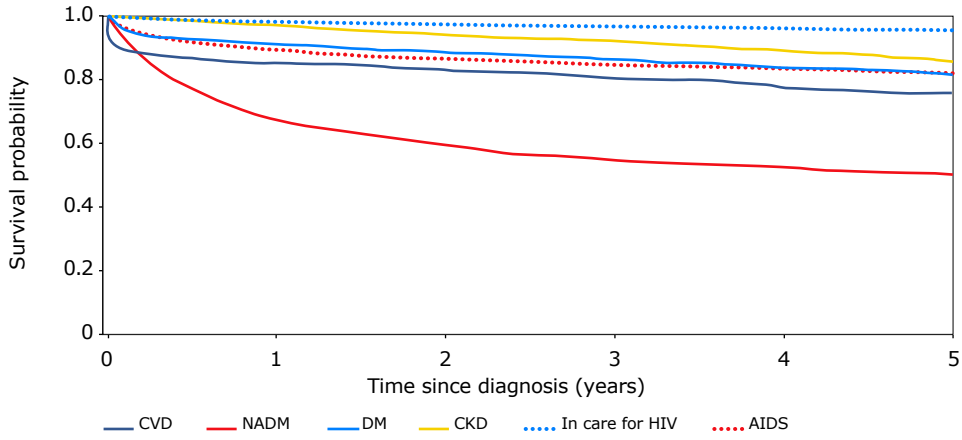
Appendix

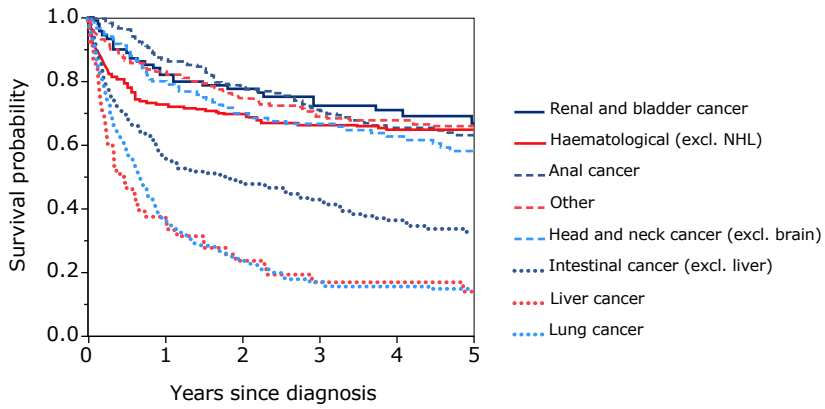
Appendix Figure 3.1: *Estimated five-year survival following the diagnosis of cardiovascular disease, non-AIDS-defining malignancy, diabetes mellitus, and chronic kidney disease. Two reference groups are included: survival from date of entry into HIV care (after 1 January 2000), and from date of first 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	1,403	1,141	1,014	880	765	657
NADM	1,330	853	665	530	430	353
DM	1,349	1,173	1,037	916	811	714
CKD	2,138	1,835	1,547	1,239	957	726
In care for HIV	21,544	19,633	18,255	17,018	15,898	14,661
AIDS	3,479	2,960	2,731	2,540	2,375	2,164

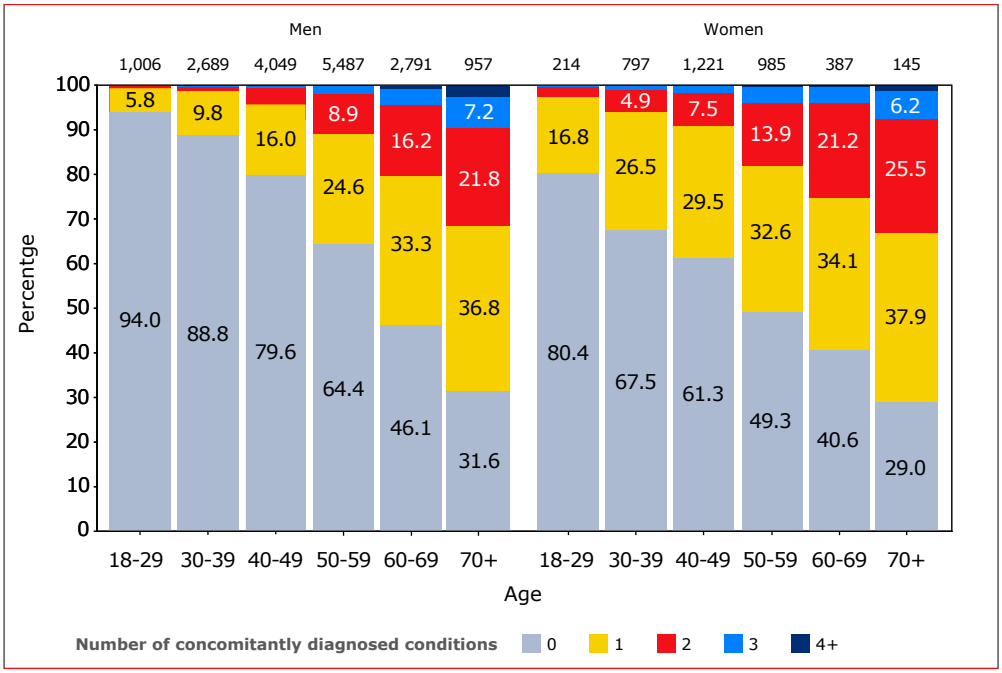
Legend: *CVD=cardiovascular disease; NADM=non-AIDS defining malignancy; DM=diabetes mellitus; CKD=chronic kidney disease.*

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 2019.*

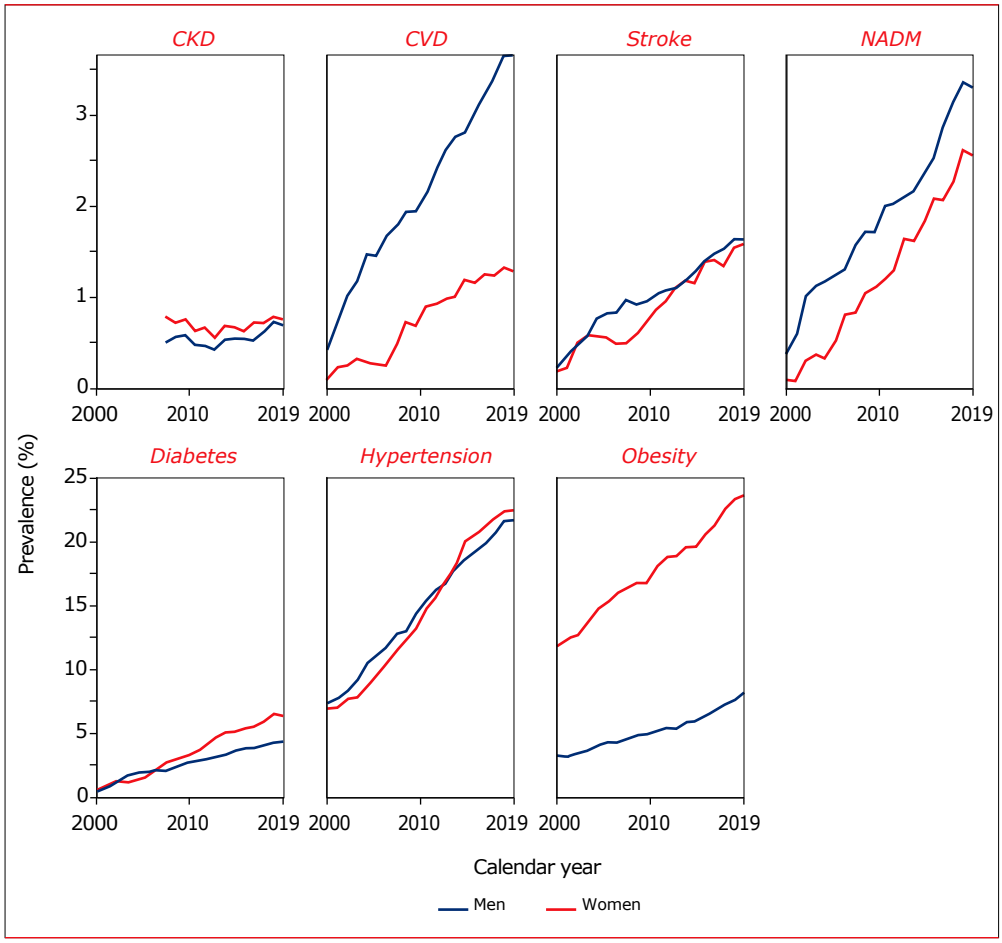


Legend: *excl.=excluding; NHL=non-Hodgkin's lymphoma.*

Appendix Figure 3.3: Prevalence of non-AIDS multimorbidity by gender in the adult population in 2019. 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.

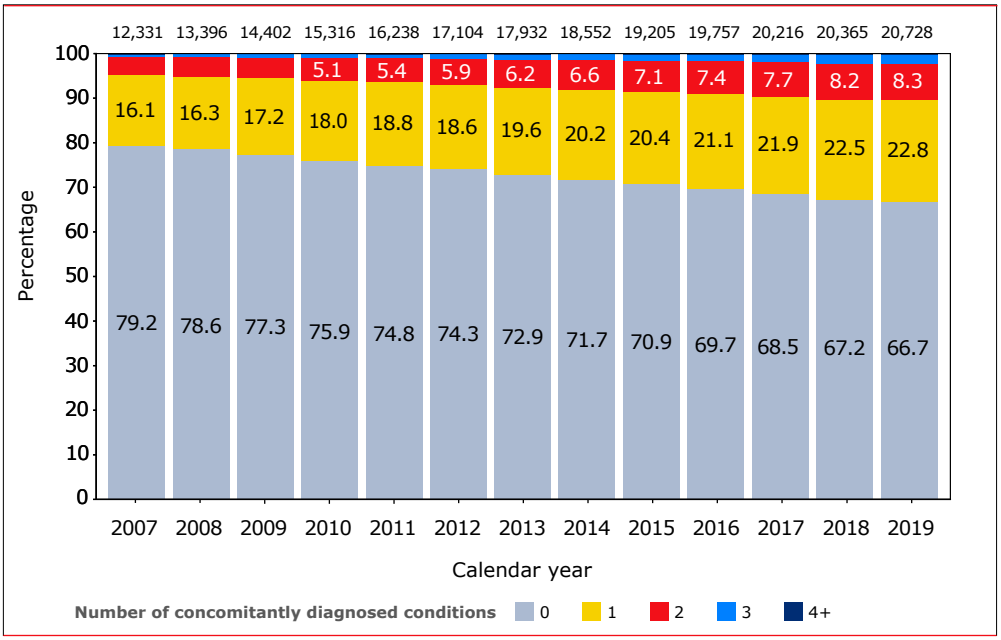


Appendix Figure 3.4: *Prevalence of non-AIDS comorbidities in the adult population between 2000 and 2019.*



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, 2001-05, 2006-10, and 2011-19.*

	Calendar period								
Causes of death	**96-00**	**01-05**	**06-10**	**11-15**	**16-19**	**2016**	**2017**	**2018**	**2019**
AIDS									
AIDS - infection	69	120	147	103	18	6	4	3	5
AIDS - malignancy	60	63	61	43	41	8	13	12	8
AIDS - unclassifiable	89	63	19	15	21	10	3	3	5
Subtotal	*218*	*246*	*227*	*161*	*80*	*24*	*20*	*18*	*18*
Non-AIDS malignancies	*30*	*95*	*136*	*193*	*210*	*49*	*62*	*48*	*51*
Cardiovascular disease									
Myocardial infarction	14	30	46	40	21	8	4	2	7
Stroke	3	11	13	11	15	7	3	3	2
Other CVD	6	24	26	50	49	16	10	15	8
Subtotal	*23*	*65*	*85*	*101*	*85*	*31*	*17*	*20*	*17*
Non-AIDS infection	*23*	*42*	*32*	*27*	*24*	*7*	*3*	*10*	*4*
Liver disease	*15*	*28*	*55*	*43*	*20*	*6*	*7*	*7*	*.*
Lung disease	*7*	*11*	*30*	*38*	*47*	*13*	*14*	*9*	*11*
Non-natural death									
Accident or violence	6	11	22	16	14	7	2	4	1
Suicide	12	30	30	52	36	10	12	11	3
Euthanasia	7	5	.	2	1	1	.	.	.
Subtotal	*25*	*46*	*52*	*70*	*51*	*18*	*14*	*15*	*4*
Alcohol and substance abuse	12	15	27	18	19	10	4	4	1
Other causes	21	24	23	43	47	13	8	18	8
Unknown	23	57	53	84	83	20	18	21	24
Total	**397**	**629**	**720**	**778**	**666**	**191**	**167**	**170**	**138**

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	1.32 (1.14-1.52)	<.001		0.97 (0.83-1.14)	0.750	
Region of birth						
Netherlands	1 (reference)		0.108	1 (reference)		0.020
Other	0.92 (0.83-1.02)	0.109		1.15 (1.02-1.30)	0.020	
HIV-1 transmission route						
Blood contact	0.71 (0.50-1.01)	0.054		0.77 (0.53-1.12)	0.170	
Heterosexual	1.08 (0.95-1.22)	0.234		0.86 (0.74-1.00)	0.057	
IDU	1.62 (1.33-1.96)	<.001		0.65 (0.50-0.84)	0.001	
MSM	1 (reference)		<.001	1 (reference)		<.001
Age*						
18-29	0.91 (0.65-1.26)	0.553	<.001	1.04 (0.84-1.28)	0.720	<.001
30-39	1 (reference)			1 (reference)		
40-49	1.53 (1.31-1.78)	<.001		1.12 (0.99-1.28)	0.079	
50-59	2.65 (2.27-3.09)	<.001		1.38 (1.19-1.61)	<.001	
60-69	4.76 (4.03-5.62)	<.001		1.41 (1.16-1.72)	<.001	
70+	10.24 (8.40-12.48)	<.001		1.89 (1.34-2.67)	<.001	
CD4 cell count**						
0-50	13.48 (11.16-16.28)	<.001	<.001	6.32 (5.07-7.87)	<.001	<.001
50-199	5.11 (4.43-5.89)	<.001		2.59 (2.18-3.06)	<.001	
200-349	2.17 (1.89-2.50)	<.001		1.49 (1.26-1.75)	<.001	
350-499	1.43 (1.24-1.65)	<.001		1.22 (1.03-1.44)	0.021	
500-749	1 (reference)			1 (reference)		
750+	0.88 (0.75-1.03)	0.101		1.10 (0.90-1.34)	0.357	
Per year longer on cART with HIV RNA >1,000 copies/ml	1.05 (1.04-1.07)	<.001	<.001	1.03 (1.01-1.06)	0.015	0.017
Treatment status at start cART						
Treatment-experienced	1.00 (0.90-1.11)	0.956		0.64 (0.56-0.73)	<.001	
Treatment-naive	1 (reference)			1 (reference)		
Prior AIDS event	1.74 (1.58-1.91)	<.001				
Hepatitis B virus positive	1.30 (1.13-1.50)	<.001		1.08 (0.89-1.31)	0.436	
Hepatitis C virus positive	1.59 (1.37-1.84)	<.001		1.32 (1.09-1.60)	0.004	

	Death			AIDS		
	RR (95% CI)	p-value	Overall p-value	RR (95% CI)	p-value	Overall p-value
Body mass index*						
<18	3.12 (2.74-3.56)	<.001	<.001			
18-25	1 (reference)					
25-30	0.66 (0.59-0.74)	<.001				
30+	0.82 (0.68-0.98)	0.028				
Smoking status						
Current smoker	1.10 (0.97-1.26)	0.144	<.001	0.75 (0.66-0.85)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	2.12 (1.87-2.40)	<.001		0.93 (0.80-1.08)	0.326	
Early cART***	0.85 (0.59-1.23)	0.390		1.18 (0.89-1.57)	0.257	

**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 2018) 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	45	2,645	17.0 (12.4–22.8)	2	223	9.0 (1.1–32.4)	9	196	46.0 (21.0–87.3)
050–199	204	9,628	21.2 (18.4–24.3)	11	642	17.1 (8.6–30.7)	35	1,084	32.3 (22.5–44.9)
200–349	425	21,364	19.9 (18.0–21.9)	18	876	20.5 (12.2–32.5)	80	1,783	44.9 (35.6–55.8)
350–499	568	41,167	13.8 (12.7–15.0)	42	1,777	23.6 (17.0–31.9)	115	3,475	33.1 (27.3–39.7)
500–749	789	88,137	9.0 (8.3–9.6)	56	4,253	13.2 (9.9–17.1)	191	7,030	27.2 (23.5–31.3)
750+	558	98,288	5.7 (5.2–6.2)	41	4,783	8.6 (6.2–11.6)	164	8,822	18.6 (15.9–21.7)

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	1,680	2.4 (0.6-6.1)	24	437	54.9 (35.2-81.7)	6	109	55.1 (20.2-119.9)
	32	5,923	5.4 (3.7-7.6)	118	1,676	70.4 (58.3-84.3)	8	304	26.3 (11.4-51.9)
	88	13,644	6.4 (5.2-7.9)	213	4,315	49.4 (43.0-56.5)	26	746	34.9 (22.8-51.1)
	128	26,514	4.8 (4.0-5.7)	258	7,570	34.1 (30.0-38.5)	25	1,830	13.7 (8.8-20.2)
	249	60,068	4.1 (3.6-4.7)	271	13,418	20.2 (17.9-22.7)	22	3,368	6.5 (4.1-9.9)
	209	69,513	3.0 (2.6-3.4)	134	11,828	11.3 (9.5-13.4)	10	3,342	3.0 (1.4-5.5)

Appendix Table 3.4: *Absolute number of first AIDS events among HIV-1-positive individuals during the periods 1996-2000, 2001-05, 2006-10, 2011-15 and 2016-19.*

CDC event	1996-2000	2001-2005	2006-2010	2011-2015	2016-2019	Total	
	n	n	n	n	n	n	%
AIDS dementia complex - HIV encefalopathy	37	47	51	44	14	193	2.98
Bacterial pneumonia, recurring	48	64	65	76	61	314	4.85
CMV disease	27	35	29	34	3	128	1.98
CMV colitis/proctitis	1	.	1	1	3	6	0.09
CMV meningo-encefalitis	.	.	.	.	1	1	0.02
CMV pneumonitis	.	.	.	.	7	7	0.11
CMV retinitis	30	20	12	12	9	83	1.28
Candidiasis lungs/bronchial/trachea	7	13	7	6	4	37	0.57
Candidiasis oesophagitis	260	237	252	222	100	1071	16.55
Cervical cancer, invasive	3	4	6	5	4	22	0.34
Coccidioimycosis, extrapulmonary / disseminated	.	.	1	.	.	1	0.02
Cryptococcosis, extrapulmonary / disseminated	21	31	33	11	10	106	1.64
Cryptosporidiosis	22	12	10	12	2	58	0.90
Cystoisosporiasis	3	9	6	.	.	18	0.28
HIV wasting	50	57	77	77	50	311	4.81
Herpes simplex virus, mucocutaneous, chronic	33	42	60	40	20	195	3.01
Histoplasmosis, extrapulmonary / disseminated	9	12	10	7	2	40	0.62
Kaposi sarcoma	154	152	186	139	65	696	10.75
Leishmaniasis visceral	.	1	2	2	2	7	0.11
Microsporidiosis	11	1	3	1	.	16	0.25
Mycobacterium other/unspecified, extrapulmo-nary / disseminated	20	13	7	10	3	53	0.82
Mycobacterium other / unspecified, pulmonary	.	3	4	9	4	20	0.31
Mycobacterium avium/kansasii, extrapulmonary / disseminated	25	19	28	9	7	88	1.36
Mycobacterium avium/kansasii, pulmonary	.	1	.	1	6	8	0.12
Non-Hodgkin's lymphoma (NHL)	59	86	80	94	45	364	5.62
Penicilliosis	.	.	1	.	.	1	0.02
Pneumocystis jirovecii extrapulmonary	1	1	3	.	1	6	0.09
Pneumocystis jirovecii pneumonia	334	299	326	262	145	1366	21.11
Primary CNS lymphoma	8	4	9	7	4	32	0.49
Progressive multifocal leucoencefalopathy	18	25	35	24	4	106	1.64
Salmonella sepsis, recurring	2	.	.	1	.	3	0.05

CDC event	1996–2000	2001–2005	2006–2010	2011–2015	2016–2019	Total	
	n	n	n	n	n	n	%
Toxoplasmosis of the brain	70	97	55	42	23	287	4.43
Tuberculosis, extrapulmonary / disseminated	78	110	81	52	16	337	5.21
Tuberculosis, pulmonary	103	175	114	70	29	491	7.59
Total	**1434**	**1570**	**1554**	**1270**	**644**	**6472**	**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 (1.12-1.41)	<.001	.	1.73 (1.41-2.13)	<.001	.
Region of birth						
Netherlands	1 (reference)	.	0.254	1 (reference)	.	0.090
Other	1.05 (0.97-1.13)	0.253	.	0.90 (0.79-1.02)	0.092	.
HIV-1 transmission route						
MSM	1 (reference)	.	<.001	1 (reference)	.	0.011
Heterosexual	1.24 (1.12-1.36)	<.001	.	1.24 (1.07-1.44)	0.004	.
IDU	1.35 (1.10-1.65)	0.004	.	1.25 (0.90-1.74)	0.190	.
Blood contact	1.27 (0.98-1.64)	0.067	.	1.19 (0.79-1.80)	0.412	.
Age*						
18-29	0.59 (0.44-0.79)	<.001	<.001	0.56 (0.31-1.05)	0.069	<.001
30-39	1 (reference)	.	.	1 (reference)	.	.
40-49	2.03 (1.78-2.31)	<.001	.	2.78 (2.15-3.58)	<.001	.
50-59	3.74 (3.28-4.27)	<.001	.	5.83 (4.53-7.50)	<.001	.
60-69	6.45 (5.59-7.44)	<.001	.	9.81 (7.52-12.81)	<.001	.
70+	10.04 (8.35-12.07)	<.001	.	16.69 (12.25-22.75)	<.001	.
CD4 cell count**						
<50	4.13 (3.22-5.28)	<.001	<.001	3.38 (2.16-5.28)	<.001	<.001
50-199	1.87 (1.59-2.18)	<.001	.	1.74 (1.35-2.25)	<.001	.
200-349	1.29 (1.15-1.44)	<.001	.	1.38 (1.16-1.66)	<.001	.
350-499	1.08 (0.97-1.19)	0.155	.	1.10 (0.94-1.30)	0.239	.
500-749	1 (reference)	.	.	1 (reference)	.	.
750+	1.18 (1.07-1.29)	<.001	.	1.31 (1.13-1.52)	<.001	.
Per year longer with CD4 <200 cells/mm^3	0.99 (0.97-1.01)	0.357	.	1.00 (0.97-1.04)	0.833	.
Prior AIDS event	1.24 (1.15-1.33)	<.001	.	1.13 (1.00-1.27)	0.052	.
Per year longer on cART while HIV RNA>1000 copies/ml	1.02 (1.00-1.04)	0.044	.	1.02 (0.99-1.05)	0.284	.
Treatment status						
Not (yet) started cART	1.20 (1.05-1.37)	0.009	<.001	1.01 (0.79-1.28)	0.951	0.032
Treatment-experienced at start cART	1.29 (1.17-1.42)	<.001	.	1.22 (1.05-1.42)	0.008	.
Treatment-naive at start	1 (reference)	.	.	1 (reference)	.	.
Per year longer on cART	1.01 (1.00-1.02)	0.035	.	1.00 (0.99-1.02)	0.476	.

	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
	1.08 (0.89–1.31)	0.454	.	1.27 (1.07–1.50)	0.005	.	0.63 (0.54–0.74)	<.001	.
	1 (reference)	.	0.016	1 (reference)	.	<.001	1 (reference)	.	<.001
	0.85 (0.74–0.97)	0.017	.	1.44 (1.27–1.63)	<.001	.	0.75 (0.67–0.84)	<.001	.
	1 (reference)	.	0.084	1 (reference)	.	<.001	1 (reference)	.	0.012
	1.03 (0.88–1.21)	0.718	.	1.53 (1.32–1.78)	<.001	.	1.01 (0.88–1.16)	0.911	.
	1.36 (1.00–1.86)	0.053	.	1.62 (1.14–2.28)	0.006	.	1.52 (1.14–2.02)	0.004	.
	1.55 (1.07–2.24)	0.020	.	1.56 (1.06–2.31)	0.024	.	1.38 (1.00–1.91)	0.049	.
	0.59 (0.34–1.02)	0.058	<.001	0.62 (0.42–0.93)	0.019	<.001	0.32 (0.14–0.75)	0.009	<.001
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	2.24 (1.76–2.84)	<.001	.	1.57 (1.30–1.89)	<.001	.	3.18 (2.34–4.30)	<.001	.
	4.25 (3.35–5.40)	<.001	.	2.51 (2.06–3.06)	<.001	.	8.51 (6.35–11.41)	<.001	.
	8.59 (6.68–11.04)	<.001	.	4.17 (3.34–5.19)	<.001	.	23.60 (17.57–31.70)	<.001	.
	14.32 (10.65–19.24)	<.001	.	4.86 (3.54–6.67)	<.001	.	46.09 (33.69–63.05)	<.001	.
	2.48 (1.50–4.10)	<.001	<.001	6.53 (4.63–9.21)	<.001	<.001	1.27 (0.63–2.59)	0.502	0.001
	1.95 (1.52–2.52)	<.001	.	1.85 (1.43–2.39)	<.001	.	1.66 (1.31–2.11)	<.001	.
	1.34 (1.12–1.61)	0.002	.	1.16 (0.96–1.41)	0.135	.	1.22 (1.04–1.43)	0.015	.
	1.11 (0.95–1.30)	0.190	.	1.01 (0.85–1.19)	0.939	.	1.03 (0.91–1.18)	0.621	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	0.93 (0.79–1.09)	0.354	.	1.30 (1.12–1.51)	<.001	.	0.96 (0.86–1.08)	0.530	.
	0.98 (0.94–1.01)	0.209	.	0.99 (0.95–1.02)	0.508	.	0.99 (0.96–1.02)	0.335	.
	1.23 (1.09–1.39)	0.001	.	1.33 (1.17–1.50)	<.001	.	1.14 (1.03–1.26)	0.012	.
	1.01 (0.97–1.04)	0.771	.	1.02 (0.98–1.05)	0.382	.	0.98 (0.95–1.01)	0.163	.
	1.25 (1.00–1.57)	0.055	0.014	1.45 (1.17–1.80)	<.001	<.001	0.40 (0.28–0.58)	<.001	<.001
	1.20 (1.03–1.41)	0.021	.	1.30 (1.11–1.54)	0.002	.	1.13 (0.98–1.30)	0.093	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	1.00 (0.99–1.02)	0.614	.	1.01 (0.99–1.03)	0.254	.	0.99 (0.98–1.00)	0.025	.

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value
Early cART within 12 months after last HIV-negative	0.85 (0.67-1.08)	0.177	.	1.20 (0.86-1.66)	0.283	.
Body mass index*						
0-18	1.45 (1.18-1.77)	<.001	<.001	1.11 (0.79-1.56)	0.547	0.160
18-25	1 (reference)	.	.	1 (reference)	.	.
25-30	1.20 (1.11-1.31)	<.001	.	0.99 (0.87-1.13)	0.886	.
30+	1.91 (1.71-2.14)	<.001	.	1.12 (0.91-1.38)	0.281	.
Hepatitis B virus positive	1.20 (1.06-1.37)	0.004	.	1.03 (0.83-1.28)	0.808	.
Hepatitis C virus positive	1.04 (0.91-1.18)	0.599	.	0.96 (0.77-1.18)	0.679	.
Hypertension	1.14 (1.06-1.23)	<.001	.	1.23 (1.10-1.38)	<.001	.
Smoking status						
Current smoker	1.38 (1.27-1.51)	<.001	<.001	1.92 (1.67-2.21)	<.001	<.001
Never smoker	1 (reference)	.	.	1 (reference)	.	.
Past smoker	1.45 (1.32-1.59)	<.001	.	1.57 (1.35-1.84)	<.001	.
Calendar year period						
2000-2010	1.37 (1.23-1.52)	<.001	<.001	1.56 (1.32-1.84)	<.001	<.001
2011-2015	1.23 (1.12-1.35)	<.001	.	1.33 (1.15-1.54)	<.001	.
2016-2019	1 (reference)	.	.	1 (reference)	.	.
Recent use of ABC***		.	.	1.64 (1.45-1.85)	<.001	.
Per year longer on LOP/r		.	.	1.01 (0.99-1.02)	0.265	.
Per year longer on IDV		.	.	1.00 (0.99-1.01)	0.769	.
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		.	.		.	.
RPVnow		.	.		.	.
BICnow		.	.		.	.

**Time-updated.*

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

****Current use or recently used in the past six 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
	0.54 (0.33-0.86)	0.009	.	0.79 (0.50-1.23)	0.295	.	1.05 (0.83-1.33)	0.700	.
	1.97 (1.50-2.58)	<.001	<.001	1.38 (0.94-2.03)	0.102	<.001	1.51 (1.14-2.01)	0.004	0.015
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	0.84 (0.73-0.97)	0.015	.	2.18 (1.89-2.52)	<.001	.	1.12 (1.00-1.25)	0.046	.
	0.94 (0.75-1.19)	0.620	.	4.82 (4.08-5.69)	<.001	.	1.19 (1.02-1.40)	0.032	.
	1.64 (1.36-1.97)	<.001	.	1.06 (0.85-1.32)	0.603	.	1.44 (1.21-1.71)	<.001	.
	1.10 (0.89-1.35)	0.380	.	1.02 (0.82-1.28)	0.852	.	1.31 (1.12-1.53)	<.001	.
	0.97 (0.86-1.09)	0.599	.	1.16 (1.03-1.30)	0.015	.	1.15 (1.04-1.26)	0.005	.
	1.49 (1.28-1.73)	<.001	<.001	0.97 (0.84-1.12)	0.665	<.001	0.84 (0.74-0.94)	0.003	0.011
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	1.81 (1.55-2.11)	<.001	.	1.26 (1.09-1.47)	0.002	.	1.00 (0.89-1.12)	0.975	.
	1.03 (0.87-1.22)	0.702	0.929	1.55 (1.29-1.86)	<.001	<.001	1.19 (1.00-1.41)	0.051	0.009
	1.02 (0.88-1.18)	0.832	.	1.45 (1.24-1.69)	<.001	.	1.20 (1.07-1.36)	0.002	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.	1.01 (1.00-1.02)	0.110	.		.	.
		.	.	1.02 (0.99-1.05)	0.175	.		.	.
		.	.	1.06 (1.03-1.09)	<.001	.		.	.
		.	.		.	.	1.00 (0.98-1.02)	0.683	.
		.	.		.	.	1.01 (1.00-1.02)	0.105	.
		.	.		.	.	1.59 (1.36-1.86)	<.001	.
		.	.		.	.	1.26 (1.06-1.50)	0.007	.
		.	.		.	.	1.71 (1.47-1.98)	<.001	.
		.	.		.	.	3.39 (3.00-3.82)	<.001	.
		.	.		.	.	1.39 (1.15-1.68)	<.001	<.001
		.	.		.	.	2.35 (1.52-3.64)	<.001	<.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 2019.*

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Aspergillosis, invasive pulmonary	6	0.2%	1	0.4%
	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis oropharyngeal	719	22.1%	67	26.8%
	Candidiasis vulvovaginal, frequent/persistent	53	1.6%	1	0.4%
	Cardiomyopathy, HIV-related	3	0.1%	0	0.0%
	Cardiomyopathy, with HIV-related component	12	0.4%	1	0.4%
	Cervical dysplasia	525	16.1%	8	3.2%
	Diarrhoea, HIV-related ≥30 days	64	2.0%	1	0.4%
	Fever e.c.i. / HIV-related	6	0.2%	0	0.0%
	HIV-associated nephropathy (HIVAN)	20	0.6%	2	0.8%
	Herpes zoster, multidermatomal	11	0.3%	0	0.0%
	Herpes zoster, recurring / multidermatomal unspecified	217	6.7%	9	3.6%
	Herpes zoster, unidermatomal recurrent	6	0.2%	2	0.8%
	Myelopathy, HIV-related	10	0.3%	0	0.0%
	Neuropathy, HIV-related	92	2.8%	2	0.8%
	Neuropathy, with HIV-related component	59	1.8%	1	0.4%
	Nocardiosis	2	0.1%	1	0.4%
	Oral Hairy Leucoplakia (OHL)	52	1.6%	2	0.8%
	Pelvic inflammatory disease	5	0.2%	0	0.0%
	Thrombocytopenia, HIV-related	100	3.1%	3	1.2%
	Thrombocytopenia, with HIV-related compo-nent	7	0.2%	3	1.2%
	Weight loss >10kg, HIV-related / unknown cause	38	1.2%	2	0.8%
Subtotal		**2008**	**61.7%**	**106**	**42.4%**
CDC-C events	AIDS dementia complex - HIV encephalopathy	44	1.4%	5	2.0%
	Bacterial pneumonia, recurring	299	9.2%	13	5.2%
	CMV disease	19	0.6%	5	2.0%
	CMV esophagitis	1	0.0%	1	0.4%
	CMV retinitis	18	0.6%	4	1.6%
	Candidiasis lungs/bronchial/trachea	10	0.3%	2	0.8%
	Candidiasis esophagitis	221	6.8%	24	9.6%
	Cervical cancer, invasive	8	0.2%	1	0.4%
	Coccidioimycosis, extrapulmonary / disseminated	1	0.0%	0	0.0%
	Cryptococcosis, extrapulmonary / disseminated	16	0.5%	5	2.0%

CD4 category										
50–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
2	0.3%	0	0.0%	0	0.0%	2	0.3%	1	0.3%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
174	29.9%	145	20.4%	118	18.9%	133	19.2%	82	20.6%
5	0.9%	9	1.3%	17	2.7%	16	2.3%	5	1.3%
0	0.0%	0	0.0%	2	0.3%	0	0.0%	1	0.3%
3	0.5%	1	0.1%	2	0.3%	3	0.4%	2	0.5%
55	9.5%	120	16.9%	106	17.0%	141	20.4%	95	23.8%
5	0.9%	17	2.4%	11	1.8%	22	3.2%	8	2.0%
1	0.2%	2	0.3%	0	0.0%	1	0.1%	2	0.5%
3	0.5%	3	0.4%	4	0.6%	4	0.6%	4	1.0%
2	0.3%	3	0.4%	2	0.3%	1	0.1%	3	0.8%
24	4.1%	54	7.6%	43	6.9%	56	8.1%	31	7.8%
0	0.0%	0	0.0%	0	0.0%	1	0.1%	3	0.8%
4	0.7%	2	0.3%	0	0.0%	1	0.1%	3	0.8%
7	1.2%	18	2.5%	25	4.0%	23	3.3%	17	4.3%
7	1.2%	9	1.3%	14	2.2%	18	2.6%	10	2.5%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
12	2.1%	10	1.4%	9	1.4%	11	1.6%	8	2.0%
0	0.0%	1	0.1%	0	0.0%	3	0.4%	1	0.3%
19	3.3%	21	3.0%	23	3.7%	22	3.2%	12	3.0%
0	0.0%	3	0.4%	0	0.0%	1	0.1%	0	0.0%
5	0.9%	9	1.3%	7	1.1%	9	1.3%	6	1.5%
329	**56.6%**	**428**	**60.3%**	**383**	**61.5%**	**468**	**67.7%**	**294**	**73.7%**
6	1.0%	8	1.1%	11	1.8%	7	1.0%	7	1.8%
50	8.6%	77	10.8%	73	11.7%	61	8.8%	25	6.3%
2	0.3%	3	0.4%	5	0.8%	1	0.1%	3	0.8%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
5	0.9%	2	0.3%	6	1.0%	1	0.1%	0	0.0%
2	0.3%	3	0.4%	1	0.2%	1	0.1%	1	0.3%
55	9.5%	50	7.0%	35	5.6%	35	5.1%	22	5.5%
1	0.2%	1	0.1%	2	0.3%	3	0.4%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
7	1.2%	3	0.4%	0	0.0%	1	0.1%	0	0.0%

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
	Cryptosporidiosis	10	0.3%	4	1.6%
	Cystoisosporiasis	1	0.0%	0	0.0%
	HIV wasting	16	0.5%	6	2.4%
	Herpes simplex virus, chronic ulcer	76	2.3%	7	2.8%
	Histoplasmosis, extrapulmonary / disseminated	4	0.1%	3	1.2%
	Kaposi sarcoma	104	3.2%	7	2.8%
	Leishmaniasis visceral	5	0.2%	1	0.4%
	Microsporidiosis	5	0.2%	2	0.8%
	Mycobacterium avium/kansasii, extrapulmonary / disseminated	21	0.6%	5	2.0%
	Mycobacterium avium/kansasii, pulmonary	3	0.1%	0	0.0%
	Mycobacterium other/unspecified, extrapulmonary / disseminated	7	0.2%	2	0.8%
	Mycobacterium other / unspecified, pulmonary	5	0.2%	0	0.0%
	Non-Hodgkin's lymphoma (NHL)	140	4.3%	7	2.8%
	Pneumocystis jirovecii extrapulmonary	1	0.0%	0	0.0%
	Pneumocystis jirovecii pneumonia	65	2.0%	20	8.0%
	Primary CNS lymphoma	5	0.2%	1	0.4%
	Progressive multifocal leucoencephalopathy	17	0.5%	5	2.0%
	Toxoplasmosis of the brain	18	0.6%	8	3.2%
	Tuberculosis, extrapulmonary / disseminated	38	1.2%	3	1.2%
	Tuberculosis, pulmonary	68	2.1%	3	1.2%
Subtotal		**1246**	**38.3%**	**144**	**57.6%**
Total		**3254**	**100.0%**	**250**	**100.0%**

CD4 category										
	50–199		200–349		350–499		500–749		750+	
	n	%	n	%	n	%	n	%	n	%
	0	0.0%	1	0.1%	3	0.5%	1	0.1%	1	0.3%
	0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
	6	1.0%	1	0.1%	2	0.3%	1	0.1%	0	0.0%
	7	1.2%	13	1.8%	18	2.9%	25	3.6%	6	1.5%
	0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
	11	1.9%	23	3.2%	22	3.5%	29	4.2%	12	3.0%
	3	0.5%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
	2	0.3%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
	7	1.2%	5	0.7%	2	0.3%	1	0.1%	1	0.3%
	0	0.0%	1	0.1%	0	0.0%	1	0.1%	1	0.3%
	1	0.2%	3	0.4%	0	0.0%	1	0.1%	0	0.0%
	2	0.3%	0	0.0%	2	0.3%	1	0.1%	0	0.0%
	34	5.9%	38	5.4%	28	4.5%	24	3.5%	9	2.3%
	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
	19	3.3%	12	1.7%	8	1.3%	4	0.6%	2	0.5%
	1	0.2%	2	0.3%	1	0.2%	0	0.0%	0	0.0%
	5	0.9%	4	0.6%	2	0.3%	1	0.1%	0	0.0%
	5	0.9%	2	0.3%	2	0.3%	1	0.1%	0	0.0%
	8	1.4%	6	0.8%	4	0.6%	10	1.4%	7	1.8%
	13	2.2%	22	3.1%	13	2.1%	11	1.6%	6	1.5%
	252	**43.4%**	**282**	**39.7%**	**240**	**38.5%**	**223**	**32.3%**	**105**	**26.3%**
	581	**100.0%**	**710**	**100.0%**	**623**	**100.0%**	**691**	**100.0%**	**399**	**100.0%**