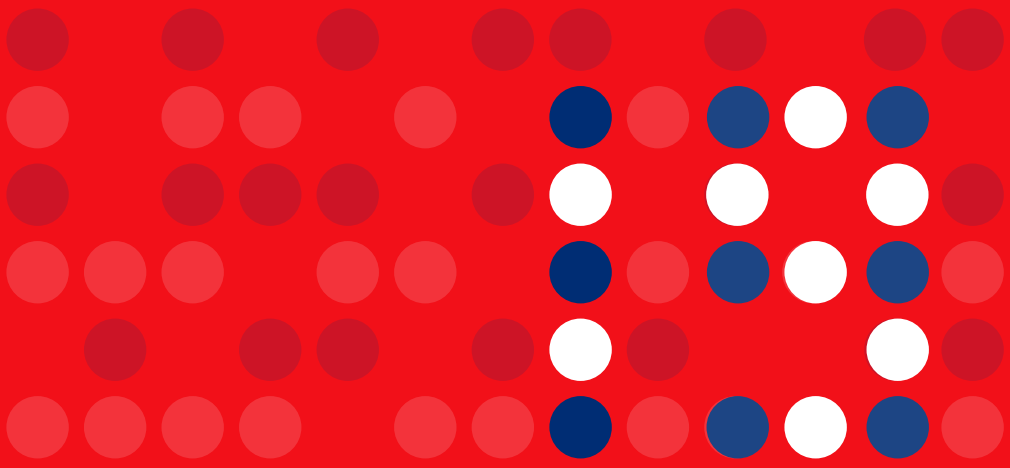
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2019

Chapter 3: HIV and non-HIV-related morbidity and mortality



About Stichting HIV Monitoring

Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, was founded in 2001 and appointed by the Dutch minister of Health, Welfare and Sport as the executive organisation for the registration and monitoring of HIV-positive individuals in the Netherlands.

In collaboration with the HIV treatment centres in the Netherlands, SHM has developed a framework for systematically collecting HIV data for the long-term follow up of all registered individuals. The Netherlands is the only country in the world to have such a framework, which enables healthcare professionals to aspire to the highest standard of HIV care.

SHM contributes to the knowledge of HIV by studying the course of the infection and the effect of its treatment. To this end, SHM follows the treatment of every HIV-positive man, woman and child in care in the Netherlands and registered in the national observational HIV cohort, ATHENA. Continuous collection of data is carried out at 24 HIV treatment centres and subcentres and 4 paediatric HIV centres in the Netherlands. Patient data are collected and entered into the database in a pseudonymised form for storage and analysis. In this way SHM is able to comprehensively map the HIV epidemic and HIV treatment outcomes in the Netherlands.

Our mission

To further the knowledge and understanding of all relevant aspects of HIV infection, including comorbidities and co-infections (such as viral hepatitis), in HIV-positive persons in care in the Netherlands.

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HIV Monitoring

Monitoring Report 2019

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

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3. HIV and non-HIV-related 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[3,4,5,6,7,8].

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[9,10,11]. For example, pulmonary hypertension[12], bone disease, and non-traumatic bone fractures[13,14,15] have 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[16,17,18]. Furthermore, 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 fat distribution (lipodystrophy), 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 causes of death for adult (18 years and older) HIV-1-positive individuals using updated Stichting HIV Monitoring (SHM) data: 26,029 adults and an additional 406 individuals who were diagnosed with HIV as children and have since become adults, now totalling 26,435 adult individuals. 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.

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) are defined according to criteria established by the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, except that Castleman's disease is also defined as a non-AIDS-defining malignancy.

Histological confirmation of malignancies is part of standard clinical practice in the Netherlands, and therefore, pathology reports have been used wherever possible 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 6 months or longer. In previous Monitoring Reports, we used a period of 3 months, but in the present Monitoring Report, we have extended the period to 6 months because of the large number of episodes of renal dysfunction that revert shortly after 3 months, and which do not represent true CKD.

Methods

For the analyses of incidence per calendar year and calendar period, we consider 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 occurred more recently. 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 2000-2005, 2006-2010, and 2011-2018, and standardised these according to the age distribution of the population during the period 2011-2018 (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

populations (period: 2011-2018) 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 occurred more recently. Subsequent follow-up time was divided into periods of 3 months. Poisson regression models were used to estimate the independent association between risk factors and each endpoint. Models were adjusted for most recent CD4 cell count (lagged by 3 months), body mass index, gender, region of birth, most likely mode of HIV-1 transmission, current age, having started cART within 12 months of being diagnosed with HIV, 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.

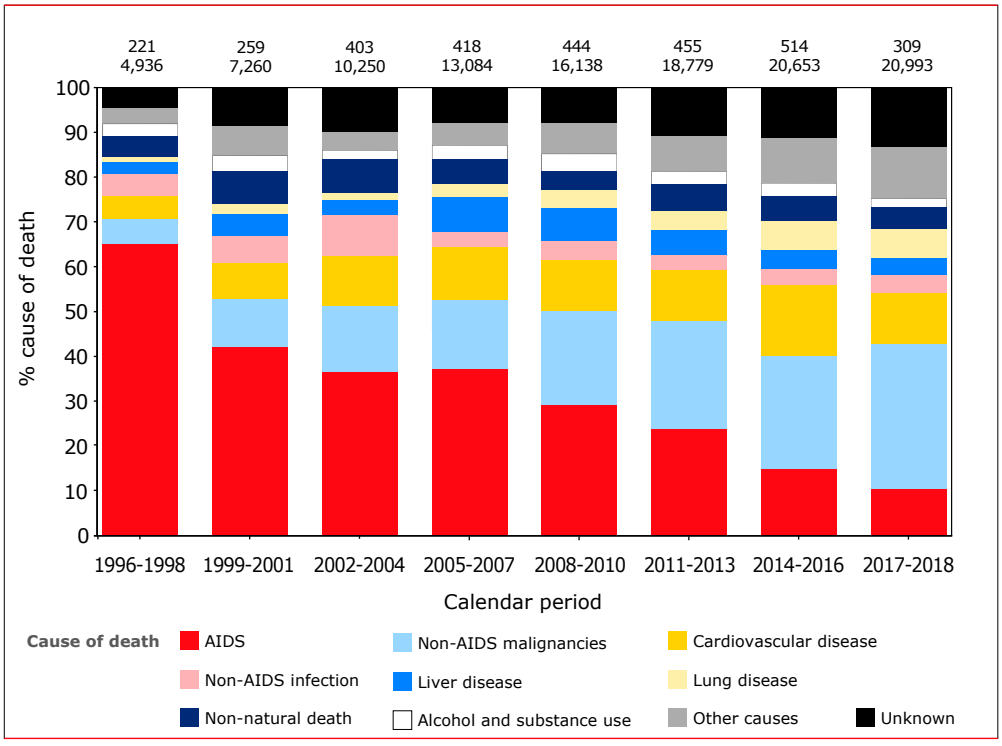
Mortality and AIDS

From 1996 onwards, the overall mortality rate in all 26,435 HIV-1-positive adults ever registered in the SHM database was 18.2 (95% confidence interval (CI) 13.5-23.9) per 1,000 person years of follow up (PYFU) in 1996 which declined to 8.4 (95% CI 7.1-9.9) per 1,000 PYFU in 2018 (*Appendix Figure 3.1A*; *Appendix Table 3.1*). Despite this improvement over time, the mortality rate in HIV-1-positive adults remains well above that expected for the general population in the Netherlands, which was 4.3 per 1,000 PYFU in 2018, when matched in terms of age and gender to our HIV-positive population. In the same group of 26,435 individuals, the incidence of AIDS decreased sharply from 120.4 (95% CI 107.9-133.9) in 1996 to 6.7 (95% CI 5.5-8.0) cases per 1,000 PYFU in 2018 (*Appendix Figure 3.1B*). The excess mortality rate can be partly ascribed to individuals who already had AIDS at the time of their HIV diagnosis. 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 7.5 (95% CI 6.2-9.1) per 1,000 PYFU in 2018.

Observed underlying causes of death are presented in *Appendix Table 3.2*. Although the AIDS-related death rate has decreased significantly since the advent of cART, it still remains substantial and is driven largely by the high number of individuals still presenting late for care with already advanced immune deficiency. Individuals who died of AIDS had lower CD4 counts (median 110 cells/mm^3 (interquartile

range, IQR 30-215)) when entering care compared to individuals who died of another cause (median 281 cells/mm^3, IQR 111-510). Thirty-three per cent of all individuals who died of AIDS between 2016 and 2018 had a CD4 cell count <50 cells/mm^3 when entering care. Among individuals who entered care with more than 300 CD4 cells/mm^3 and died of AIDS, the cause of death was relatively more likely to be an AIDS-related malignancy (70%) than among individuals who entered care with less than 50 CD4 cells/mm^3 (38.9%). The time between entry into care and death was significantly shorter in individuals who died of AIDS (median 3.3 years, IQR 0.6-8.7) than in individuals who died of a non-AIDS cause (median 8.9 years, IQR 4.5-14.9; p<0.001). Conversely, the proportion and absolute number of deaths due to non-AIDS-defining conditions have significantly increased over time (*Figure 3.1*), primarily as a consequence of the increasing size and average age of the Dutch HIV-positive population.

Figure 3.1: *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 death in individuals from the moment of starting cART. After correction for all variables listed in *Appendix Table 3.3*, including time-updated age and time-updated lagged CD4 cell counts, the risk ratios for a number of possible risk factors are presented. In general, men were more likely to die than women, and an individual's risk of death increased if they were older, belonged to the HIV transmission risk group of people who use/used injecting drugs (PWUID), had been pre-treated with nucleoside-analogue reverse transcriptase inhibitors (NRTIs) before the start of cART, 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 (although the risk of death was even higher when their CD4 cell count was less than 200 cells/mm^3).

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 (as well as other individuals not born in the Netherlands with the exception of those born in Surinam or the Dutch Antilles) having been lost to follow up (*Appendix Table 3.4*). In native Dutch individuals and those from Surinam and the Dutch Antilles, the risk of becoming lost to follow up was not dependent on their CD4 count. On the other hand, people from all other non-Dutch groups were far more likely to become lost to follow up if they had very low CD4 counts. An explanation for this observation could be that these people often return to their families in their country of origin when they experience a severe deterioration in health. As such, it is likely that the high rates of loss to follow up in non-Dutch individuals with very low CD4 counts have led to underestimation of the mortality rate in these groups.

The incidence of the first occurrence of any AIDS-defining event after entering care was 22.5 events per 1,000 PYFU of follow up. *Appendix Table 3.5* gives an overview of the AIDS events occurring between 1996 and 2018. The most common AIDS events between 2011 and 2018 were *Pneumocystis jirovecii* pneumonia (21% of all events), oesophageal candidiasis (17%), Kaposi's sarcoma (11%), tuberculosis (pulmonary 8%, extrapulmonary 5%), lymphoma (6%), toxoplasmosis of the brain (5%), AIDS-related wasting (5%), recurrent bacterial pneumonia (5%), AIDS dementia complex/HIV encephalopathy (3%) and cytomegalovirus-associated end organ disease (2%). Risk factors for AIDS-defining events are shown in *Appendix Table 3.3*.

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 start of cART were heavily influenced by events occurring shortly after the start of cART and/or while HIV-1 viraemia was still detectable, we also analysed the incidence of CDC-B and AIDS-defining events in the period between 2000 and 2018 in individuals who had started cART at least 1 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, focusing on those individuals with an optimal response to cART. Events were classified into CD4 strata based on the current CD4 and 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 from the analysis. Between 1 January 2000 and 31 December 2018, 22,768 individuals contributed a total of 181.9 thousand PYFU, during which 3,060 HIV-related events were diagnosed, resulting in an incidence rate of 16.8 events per 1,000 PYFU (1,878 CDC-B events, 10.3 events/1,000 PYFU; 1,182 CDC-C/AIDS events, 6.5 events/1,000 PYFU) (*Table 3.1*). 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 11.9 and 5.5 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 3.3 (2.9-3.8) and 2.0 (1.6-2.5)/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 3.8* shows the type and number of HIV-related diagnoses by CD4 strata).

Table 3.1: CDC-B and CDC-C/AIDS events occurring in individuals on cART while having an undetectable viral load between 2000 and 2018.

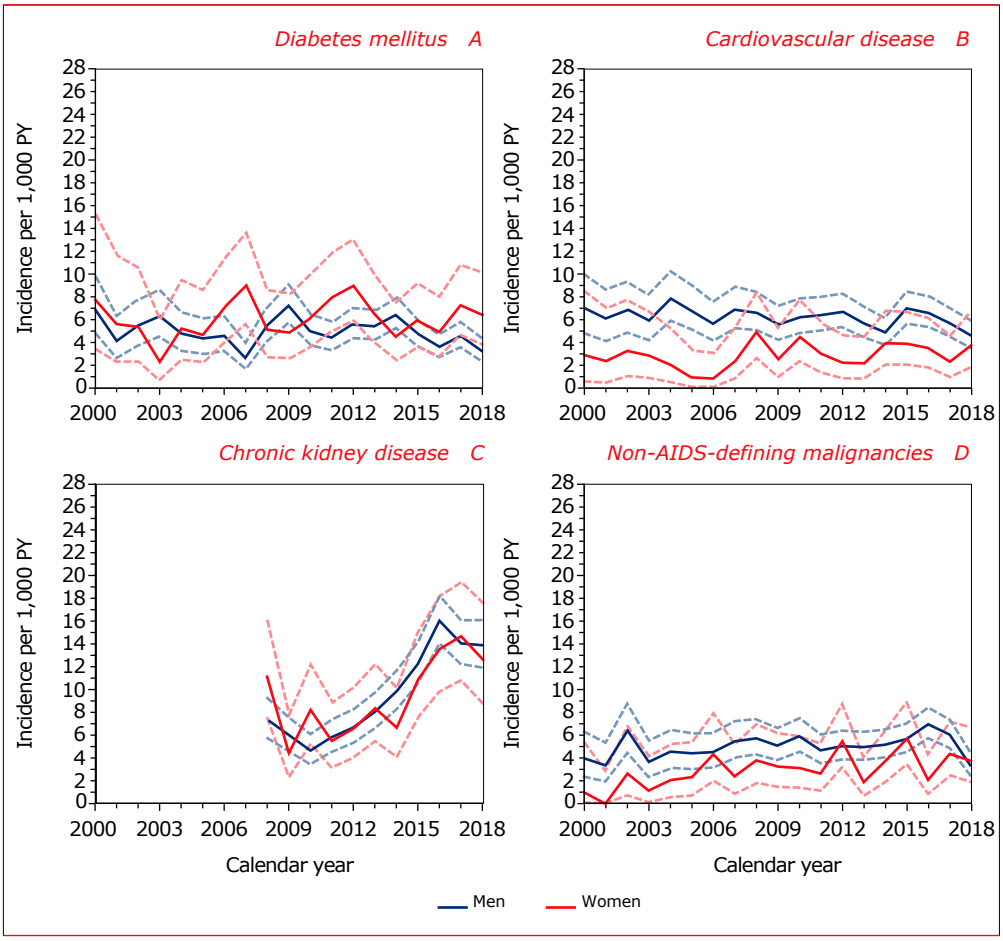
CD4 category (cells/mm³)	CDC events (n)	CDC-B events (n)	CDC-C events (n)	PYFU (x 1000)	Incidence rate CDC events (/1000 PY) (95% CI)	Incidence rate CDC-B events (/1000 PY) (95% CI)	Incidence rate CDC-C events (/1000 PY) (95% CI)
0-50	223	89	134	0.4	511 (446-583)	204 (164-251)	307 (257-364)
50-199	566	317	249	7.5	75.1 (69.0-81.5)	42.0 (37.5-46.9)	33.0 (29.1-37.4)
200-349	683	405	278	23.3	29.3 (27.2-31.6)	17.4 (15.7-19.2)	11.9 (10.6-13.4)
350-499	593	377	216	39.5	15.0 (13.8-16.3)	9.55 (8.61-10.6)	5.47 (4.77-6.25)
500-749	641	431	210	64.1	9.99 (9.24-10.8)	6.72 (6.10-7.39)	3.27 (2.85-3.75)
750+	354	259	95	47.0	7.53 (6.77-8.36)	5.51 (4.86-6.23)	2.02 (1.64-2.47)
Total	3,060	1,878	1,182	181.9	16.8 (16.2-17.4)	10.3 (9.86-10.8)	6.50 (6.13-6.88)

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 26,435 HIV-1-positive adults ever registered with SHM, 26,087 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 (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 3.2*; *Appendix Table 3.6A-H*).

Figure 3.2: 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 26,087 individuals aged 18 years or older and in follow up in or after January 2000, a total of 1,248 (956 men and 292 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.2A*) and, in 2018, was 3.2 (95% CI 2.3-4.3) per 1,000 PYFU of follow up in men and 6.4 (95% CI 3.8-10.1) per 1,000 PYFU in women. In both men and women, the incidence increased with older age (*Appendix Table 3.6A*). In men, the age-standardised incidence ratio declined over time and was significantly lower in 2011-2018 than in 2000-2005 and 2006-2010, whereas in women, the age standardised incidence in 2000-2005 and 2006-2010 was not significantly different from that in 2011-2018 (*Table 3.2*).

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, having acquired 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 3.7*). Moreover, the risk of new-onset diabetes in the periods 2000-2005 and 2006-2010 was significantly higher than in the period 2011-2018. Finally, a longer time on zidovudine was also significantly associated with an increased risk.

Table 3.2: *Crude incidence of diabetes mellitus per 1,000 person years of follow up during 2000-2005, 2006-2010 and 2011-2018 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)
2000-2005	5.2 (4.5-6.1)	1.43 (1.23-1.64)	5.0 (3.7-6.6)	0.82 (0.59-1.06)
2006-2010	5.1 (4.5-5.8)	1.23 (1.08-1.39)	6.4 (5.1-7.9)	1.03 (0.81-1.25)
2011-2018	4.8 (4.4-5.2)	1 (reference)	6.5 (5.6-7.6)	1 (reference)

**Standardised according to the observed age distribution between 2011-2018.*

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

Cardiovascular disease

From January 2000 onwards, 1,340 individuals (1,197 men and 143 women) had a fatal or non-fatal cardiovascular event (688 had myocardial infarction, 476 stroke, 96 coronary artery bypass graft, 478 coronary angioplasty or stenting, and 11 carotid endarterectomy). The crude incidence over time remained stable and was lower in women than in men (*Figure 3.2B*). The incidence in both men and women increased with older age (*Appendix Table 3.6B*). The standardised incidence ratio in men declined over time, whereas in women the standardised incidence in 2000-2005 and 2006-2010 was not significantly different from that in 2011-2018 (*Table 3.3*).

In the analysis of risk factors, those associated with cardiovascular disease were male gender, Dutch origin, older age, acquiring HIV through MSM contacts or through injecting drug use, a latest CD4 cell count <350 cells/mm^3, having a prior AIDS diagnosis, having been pre-treated with NRTIs before starting cART, use of abacavir (either currently or in the last 6 months), current and past smoking, and presence of hypertension. Cardiovascular risk was also higher during 2000-2005

and 2006-2010 than during 2011-2018, independent of other variables included in the analysis (*Appendix Table 3.7*). 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 1.56 to one of 1.42, 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 1.07 (95% CI 0.93-1.24), p=0.35; at 30-60 ml/min the IRR was 1.80 (1.44-2.25), p<0.001; at 15-30 ml/min, the IRR was 4.21 (2.67-6.63) p<0.001; and at 0-15 ml/min the IRR was 4.42 (2.41-8.13), p<0.001.

From January 2000 onwards, 169 men and 14 women experienced a fatal or non-fatal secondary cardiovascular event (116 had myocardial infarction, 74 had stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2018 in men and women with a prior cardiovascular event was 27.9 (95% CI 23.9-32.4) and 17.2 (95% CI 9.4-28.9), respectively. The crude rate and age-standardised incidence ratio (SIR; indirect method) of secondary myocardial infarction and stroke per 1,000 PYFU did not change significantly during 2000-2005 (crude rate: 36.4 events per 1,000 PYFU; SIR: 1.49, 95% CI 0.99-1.98) and 2006-2010 (crude rate: 28.2 events per 1,000 PYFU; SIR: 1.15, 95% CI 0.81-1.49) compared with the reference period 2011-2018 (crude rate: 23.9 events per 1,000 PYFU).

Table 3.3: *Crude incidence of cardiovascular disease per 1,000 person years of follow up between 2000–2005, 2006–2010, and 2011–2018 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)
2000–2005	6.8 (6.0–7.8)	1.70 (1.48–1.91)	2.3 (1.4–3.5)	1.07 (0.62–1.52)
2006–2010	6.2 (5.5–6.9)	1.29 (1.15–1.44)	3.1 (2.2–4.3)	1.26 (0.87–1.64)
2011–2018	6.0 (5.5–6.5)	1 (reference)	3.1 (2.5–3.9)	1 (reference)

**Standardised according to the observed age distribution between 2011–2018.*

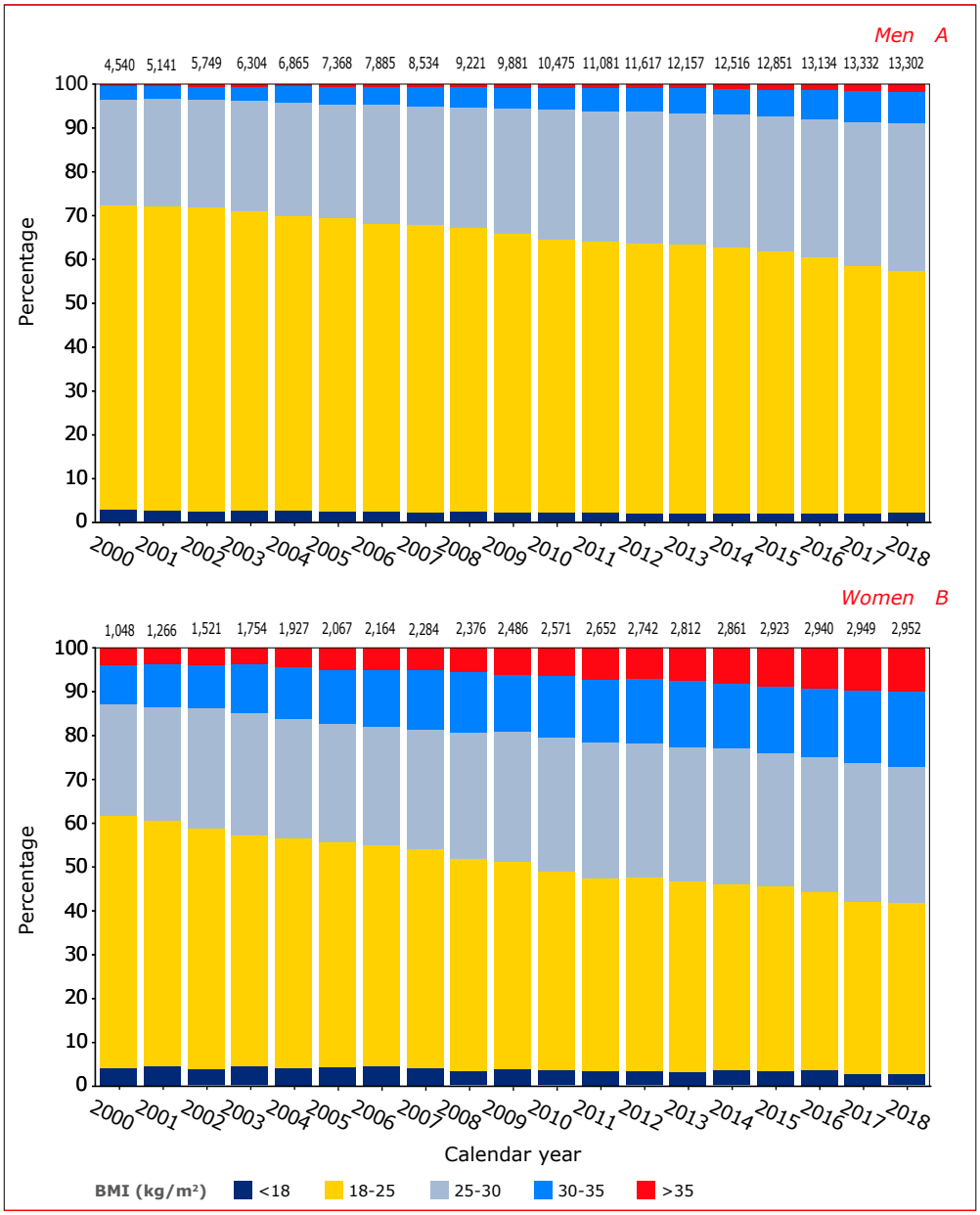
Legend: *CI=confidence intervals; PYFU=person years of follow up.*

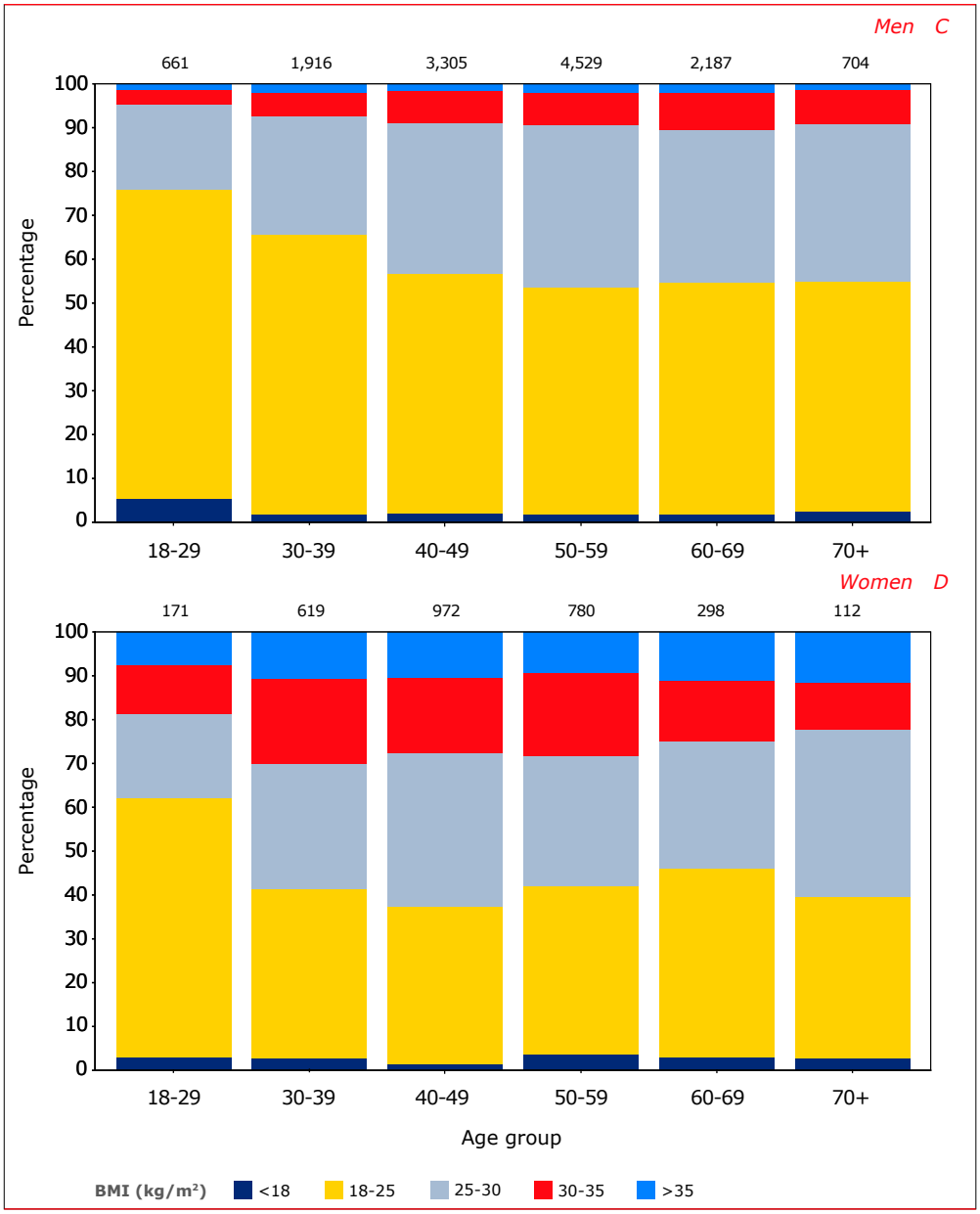
Trends in cardiovascular risk factors

Figures 3.3A and *3.3B* 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 2018, the percentage of overweight (25-30 kg/m^2) and obese (class I: 30-35 and class II: ≥35 kg/m^2) men with an available BMI measurement was 34%, 7% and 2%, respectively. In women, these percentages were 31%, 17% and 10%, respectively. Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the HIV-positive population. This analysis revealed that the increase in BMI over time 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. *Figures 3.3C* and *3.3D* show the distribution of BMI over the age groups for men and women separately in 2018. Whereas in adult men of all age groups the proportion classified as obese (9%) was substantially lower than in the general Dutch male population (13.0%), in women of all age groups there was more obesity (27%) than in the general Dutch female population (16.9%)[25].

Figure 3.4A shows that, in 2018, 47% 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 were using antihypertensives. In 2018, 23% of individuals not using antihypertensives had grade 1-3 hypertension (*Figure 3.4B*). For 3,249 of these 3,551 individuals, a 5-year cardiovascular disease (CVD) risk could be calculated with the recalibrated D:A:D study algorithm[26]. Of the 3,249 individuals, 5.3% had a 5-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 3.5* 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%) 5-year risk were 12% and 5%, respectively, which consistently increased to 20% and 12%, respectively, in 2018. The increase in the percentage of individuals at high or very high risk likely reflects the ageing of the population under study.

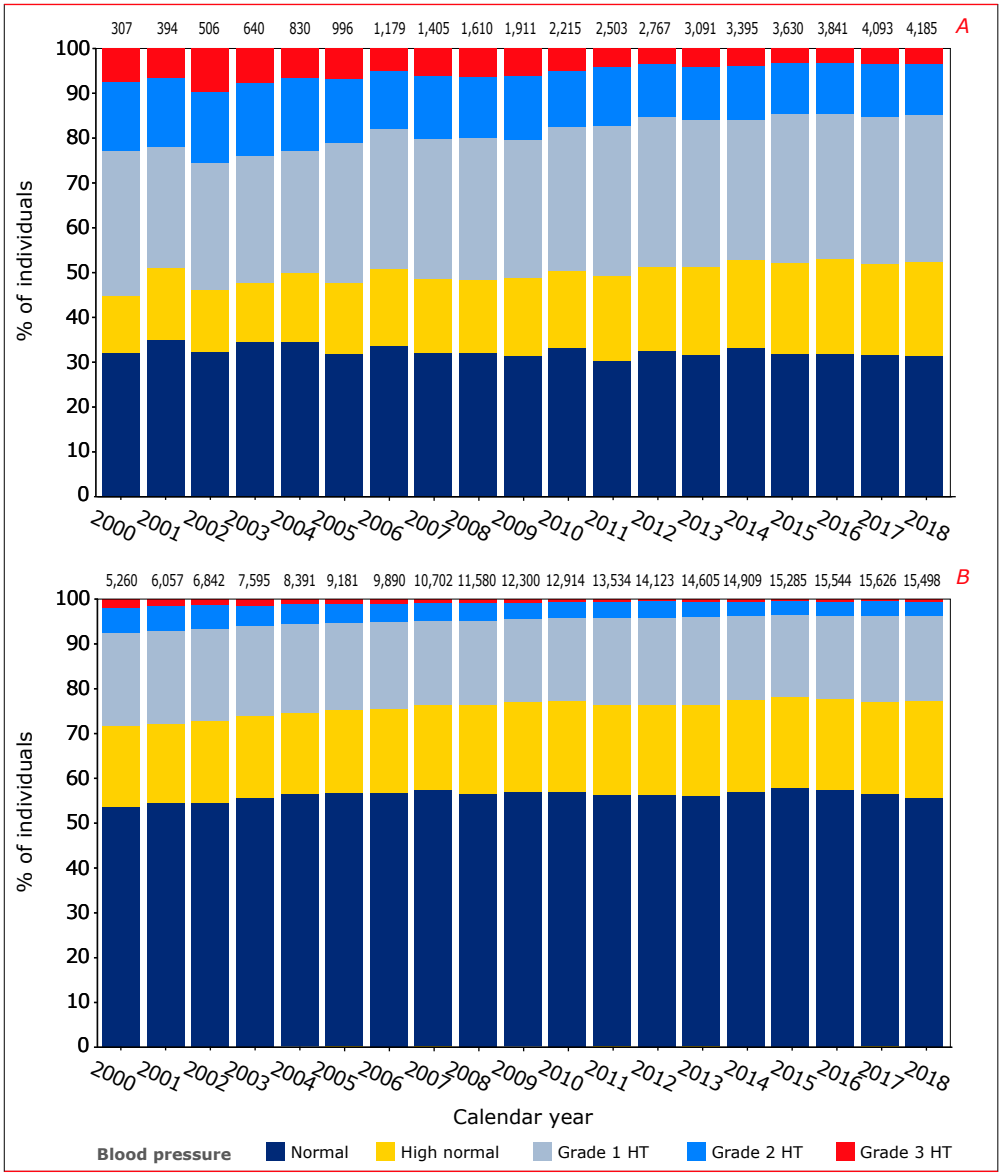
Figure 3.3: Distribution of the body mass index (BMI) at the end of each calendar year in (A) men and (B) women as a percentage of the total number of men and women with a known BMI in each year, and distribution of the BMI over the age groups for (C) men and (D) women in 2018. For each individual, the 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 age group (C & D).





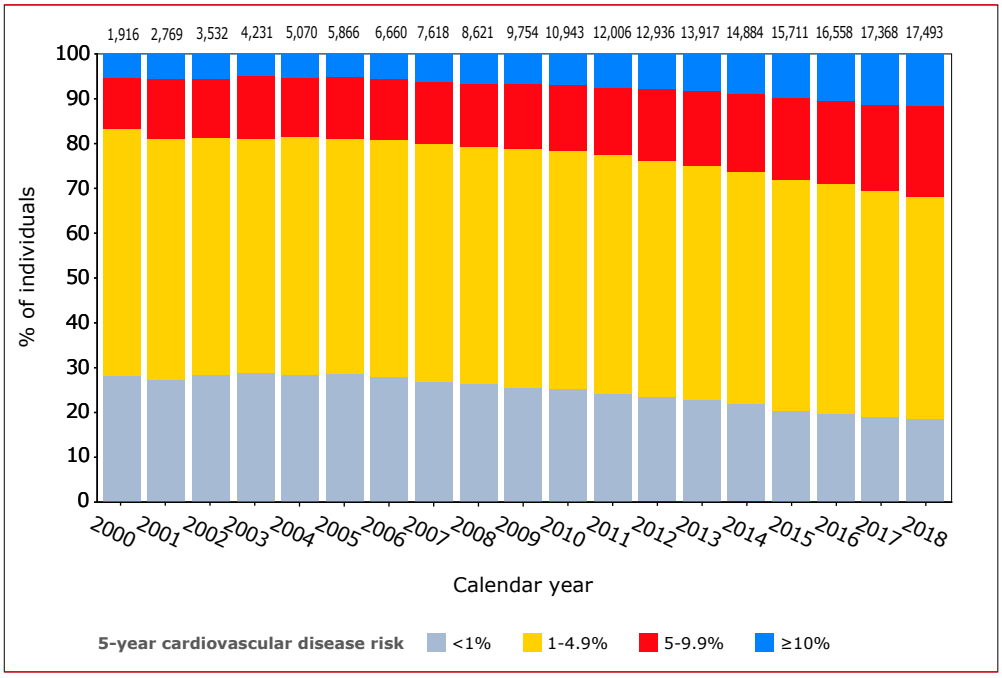
Legend: BMI=body mass index.

Figure 3.4: 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 of 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 3.5: 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.



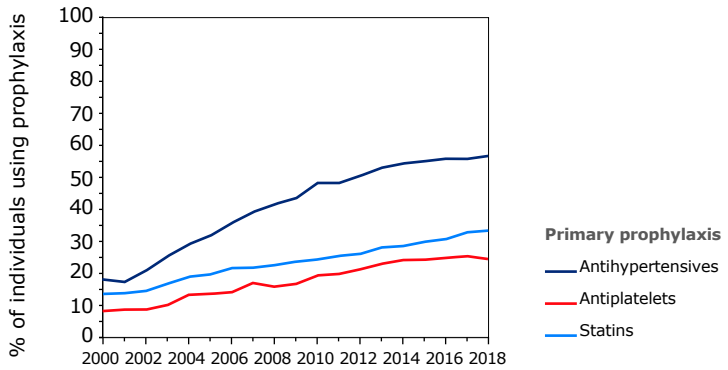
Use of primary or secondary prophylaxis for myocardial infarction or stroke

Primary prophylaxis

According to EACS guidelines, statin therapy should be offered to individuals with type 2 diabetes or a 10-year CVD risk ≥10%; 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 10-year CVD risk ≥20%; and acetylsalicylic acid should be offered to individuals aged 50 years or more with a 10-year CVD risk ≥20%[29].

Figure 3.6 shows the trends in the use of these medications in these target populations for individuals without a prior stroke, myocardial infarction, or cardiovascular surgical procedure. The percentage of individuals for whom primary prophylaxis using statins and the above-mentioned antihypertensive agents (referred to collectively hereafter as antihypertensives) is recommended has increased over time, although these percentages seem to have levelled off somewhat since 2012. Although the percentage of individuals at high risk aged 50 years or older who used acetylsalicylic acid/clopidogrel as primary prevention increased slowly up to 2014, the overall proportion remains minimal and has remained stable during the last 4 years.

Figure 3.6: *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 as primary prophylaxis for myocardial infarction or stroke.*

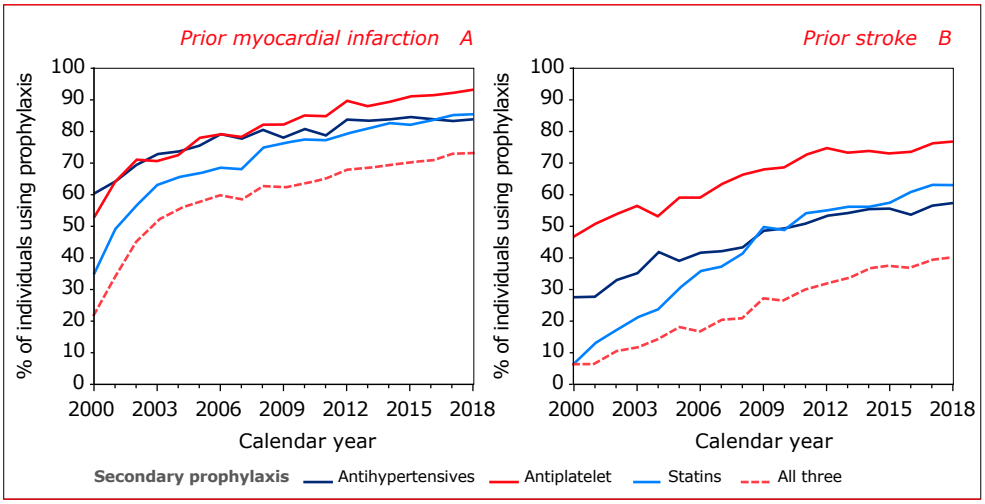


Secondary prophylaxis for myocardial infarction or stroke

According to all guidelines, individuals with a prior myocardial infarction or ischaemic stroke should receive lifelong treatment with statins, ACE inhibitors, or beta blockers or angiotensin receptor blockers (referred to here as antihypertensives), as well as low-dose acetylsalicylic acid/clopidogrel[30,31]. *Figure 3.7A* shows that the percentages of individuals using statins, acetylsalicylic acid/clopidogrel, or antihypertensives after a myocardial infarction increased between 2000 and 2018: in 2018, 86% of individuals with a prior myocardial infarction used statins, 84% used antihypertensives, and 93% used acetylsalicylic acid/clopidogrel. Although the use of statins and antihypertensives after an ischaemic stroke also

increased over time, in 2018 these medications were used less frequently after stroke than after a myocardial infarction (63% for statins, 77% for acetylsalicylic acid/clopidogrel, and 58% for antihypertensives) (*Figure 3.7B*).

Figure 3.7: *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 *Figure 3.8*. The percentage of individuals with normal kidney function decreased over time from 76% in 2007 to 48% in 2018. This decrease was observed in both men and women (*Figure 3.9*). Typically, eGFR

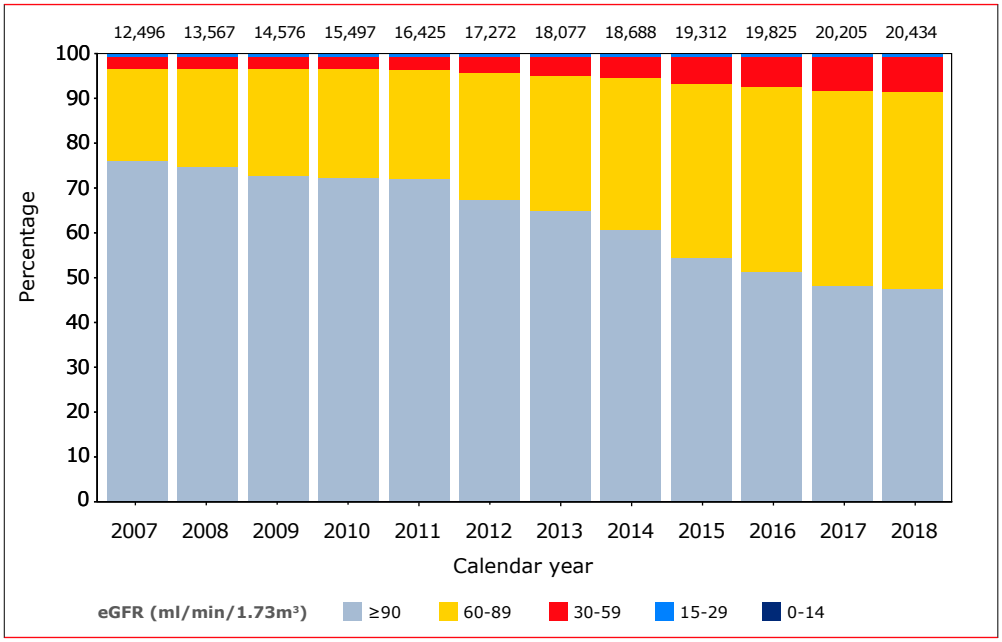
decreases with increased age, as shown in *Figure 3.10*, and therefore, the decrease in the proportion of individuals with normal function over time is likely to partly reflect the increasing age of individuals in care.

CKD incidence and risk factors

In individuals with an eGFR >60ml/min/1.73m^2 at inclusion in the analyses and without 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 3.2C*). 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 5.8 cases per 1,000 PYFU in the period 2008-2010 to 10.8 in 2011-2018, and in women the incidence rose from 8.2 to 10.1 cases per 1,000 PYFU during the same periods (*Table 3.4*). The standardised incidence ratio in men, but not in women, increased significantly over time (*Table 3.4*).

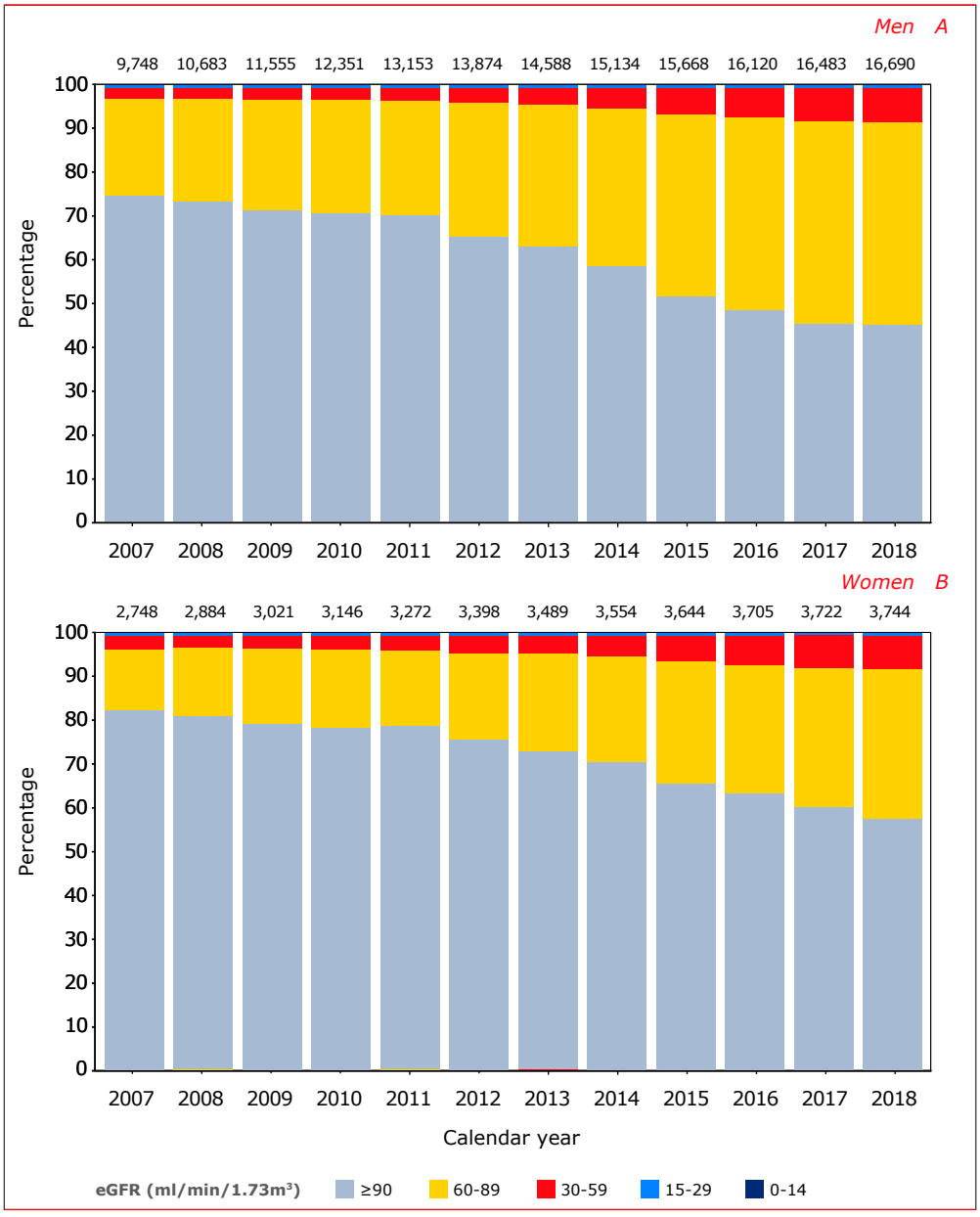
Risk factors for CKD included female gender, Dutch origin, low current CD4 cell count (<200 cells/mm^3), a prior AIDS diagnosis, belonging to the HIV transmission risk group of people who inject drugs, older age, lower body mass index, hypertension, diabetes mellitus, cardiovascular disease, pre-treatment with monotherapy and dual therapy with nucleoside analogues before the start of cART, and chronic HBV and HCV co-infection (*Appendix Table 3.7*). When current use of cobicistat, rilpivirine, dolutegravir and bictegravir were added to the model, the increased risk of CKD in the calendar period 2011-2018 disappeared in comparison to that in 2008-2010. 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 therefore do not truly reflect an increase in CKD.

Figure 3.8: Distribution of categories of estimated glomerular filtration rate (eGFR) at the end of each calendar year as a percentage of the total number of individuals with an available creatinine measurement. For each individual, the last 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.

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



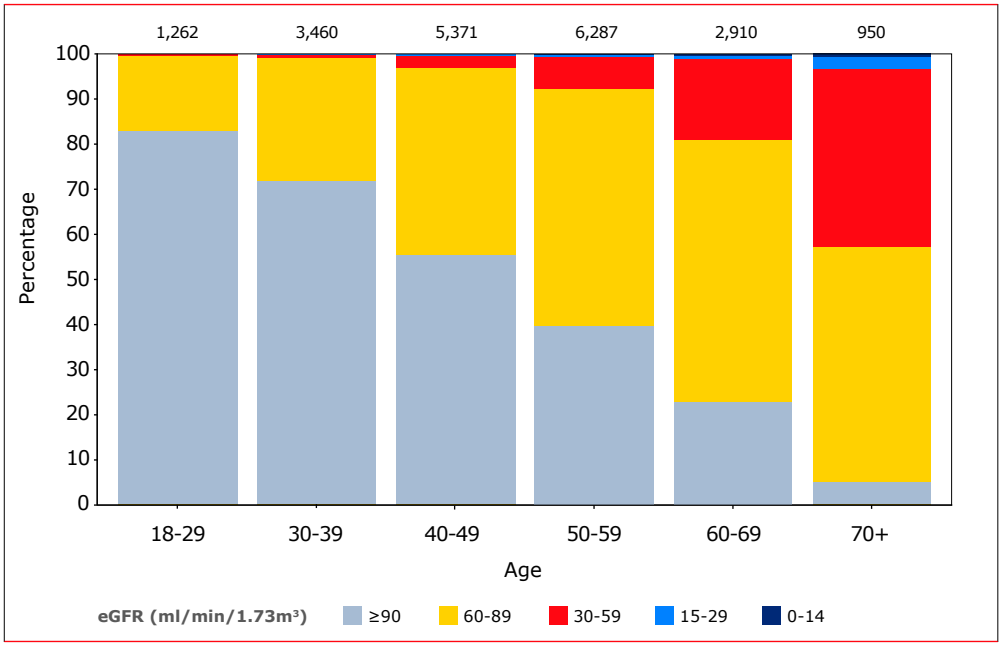
Legend: *eGFR=estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60-89 ml/min/1.73m²: mildly reduced; 30-59 ml/min/1.73m²: moderately reduced; 15-29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

Table 3.4: Crude chronic kidney disease incidence per 1,000 person years of follow up between 2008-2010 and between 2011-2018 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)
2008-2010	5.8 (4.7-7.2)	0.67 (0.53-0.80)	8.2 (5.7-11.4)	1.20 (0.80-1.60)
2011-2018	10.8 (10.1-11.6)	1 (reference)	10.1 (8.6-11.8)	1 (reference)

**Standardised according to the observed age distribution between 2011-2018.*
***Legend:** CI=confidence interval; PYFU=person years of follow up.*

Figure 3.10: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2018 for different age categories. For each individual, the last available measurement in 2018 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 2018, 1,495 diagnoses of non-AIDS-defining malignancy in 1,401 unique individuals were recorded in SHM's database. An additional 638 individuals were diagnosed with one or more non-melanoma skin cancers, but these were not

included in the present analysis. *Table 3.5* shows the most common types of non-AIDS-defining cancer: lung cancer (18%), haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 16%), invasive anal cancer (13%), intestinal cancer (excluding liver cancer, 11%), head and neck cancers (8%), and prostate cancer (8%). *Figure 3.11* shows the relative changes in types of non-AIDS-defining cancers over time. The proportion of individuals with intestinal, prostate and renal cancer has increased over time, possibly 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 increased slightly from 5.8 cases per 1,000 PYFU in 2000-2005 to 6.5 cases per 1,000 PYFU in 2011-2018, and in women from 2.0 in 2000-2005 to 4.0 cases per 1,000 PYFU in 2011-2018 (*Figure 3.2D*; *Appendix Table 3.6D*). However, when the changes in the age distribution of the HIV-positive population were taken into account, the age-standardised incidence in men was actually statistically significantly lower in the period 2011-2018 compared to 2000-2005 and 2006-2010 (*Table 3.6*). 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. In women, the age-standardised incidence was (borderline significantly) lower in the period 2011-2018 than in 2006-2010, but not 2000-2005 (*Table 3.6*).

Demographic and clinical factors independently associated with an increased risk of a first non-AIDS-defining malignancy were older age, having acquired 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 and/or past smoking (*Appendix Table 3.7*). Furthermore, people who had not yet started cART or who had been pre-treated with mono- or dual-nucleoside analogue RT inhibitors prior to starting CART had an independently increased risk for NADM compared with those who started cART while being treatment naïve (risk ratio (RR) 1.23 (1.04-1.46)). 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 0.46, 95% CI (0.27-0.80), p<0.001) 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).

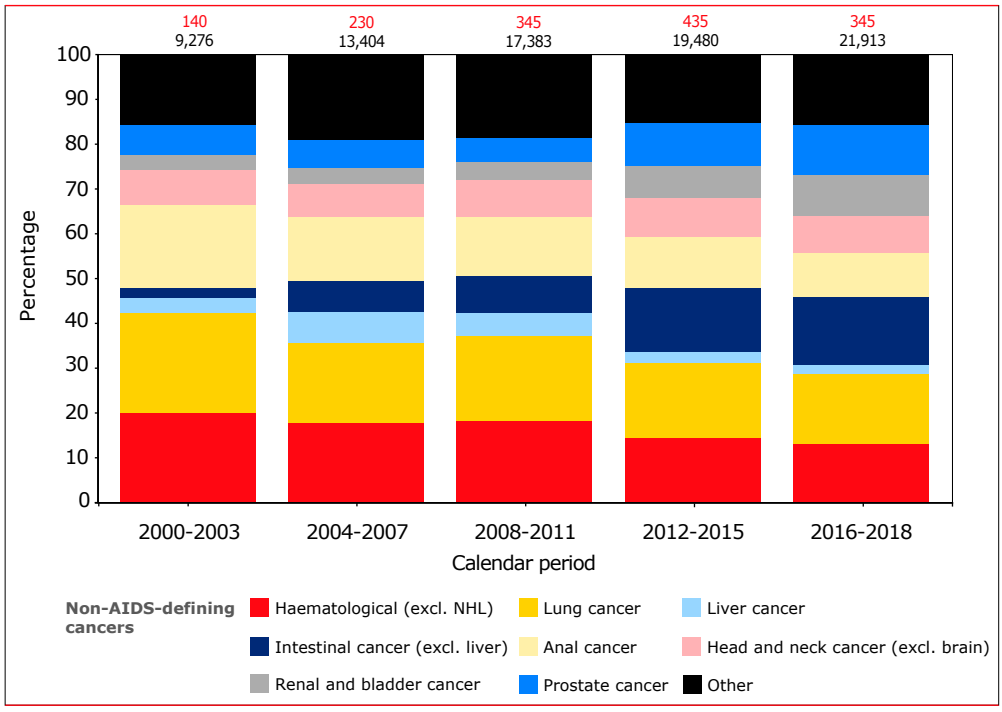
In the period from 1 January 2000 to 31 December 2018, the 5-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 50.1%, compared with 73.0% for CVD, 81.5% for DM, and 85.7% for CKD (*Appendix Figure 3.2*). In the same period, the

5-year survival rate of adults newly-entering care in one of the Dutch HIV treatment centres was 95.5%, and 82.1% for those newly entering care with an AIDS diagnosis. The 5-year survival rates following the most common non-AIDS-defining malignancies are shown in *Table 3.5* and *Appendix Figure 3.3*.

Anal cancer

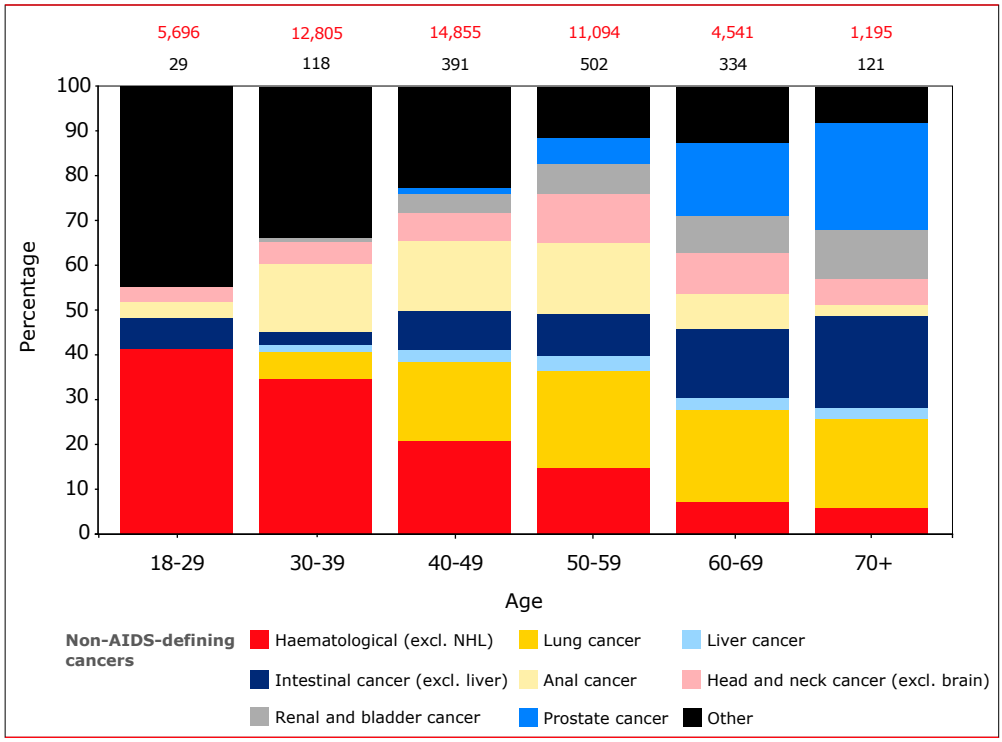
In total, 6 HIV-positive women and 182 HIV-positive men were diagnosed with anal cancer. Among HIV-positive men, the incidence of anal cancer fluctuated around 0.7 cases per 1,000 PYFU between 2000 and 2018 (*Figure 3.2G*). A 2015 study exploring the incidence of anal cancer among HIV-1-positive individuals 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=18) to analyse.

Figure 3.11: *Relative changes in non-AIDS-defining malignancies between 2000 and 2018 in HIV-1-positive individuals in the Netherlands. The numbers in red at the top of each bar represent the number of non-AIDS-defining cancer diagnoses during that calendar period, the numbers in black represent the number of individuals contributing data during that calendar year.*



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 in red at the top of each bar represent the number of cancer diagnoses in that age category, the numbers in black represent the number of individuals contributing data in that age category between 2000 and 2018.



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

Table 3.5: Most common non-AIDS-defining malignancies diagnosed between 2000-2018, 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	263	17.6	14.2
Haematological cancer (excluding non-Hodgkin's lymphoma)	240	16.1	63.3
Anal cancer	188	12.6	62.1
Intestinal cancer (excluding liver)	162	10.8	36.3
Head and neck cancer (excluding brain)	124	8.3	57.1
Prostate cancer	120	8.0	78.0
Other cancers	90	6.0	48.8
Renal and bladder cancer	89	6.0	69.0
Malignant melanoma	64	4.3	69.4
Liver cancer	57	3.8	13.3
Breast cancer	39	2.6	82.6
Testicular cancer	31	2.1	89.1
Gynaecological cancer (excluding cervical)	23	1.5	66.0
Central nervous system (CNS) cancer	5	0.3	50.0

Table 3.6: Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up between 2000-2005, 2006-2010, and 2011-2018, 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)
2000-2005	5.8 (5.0-6.6)	1.33 (1.15-1.51)	2.0 (1.2-3.1)	0.79 (0.44-1.15)
2006-2010	6.9 (6.2-7.6)	1.34 (1.19-1.48)	3.9 (2.9-5.2)	1.29 (0.94-1.64)
2011-2018	6.5 (6.1-7.0)	1 (reference)	4.1 (3.4-5.0)	1 (reference)

**Standardised according to the observed age distribution between 2011-2018.*

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

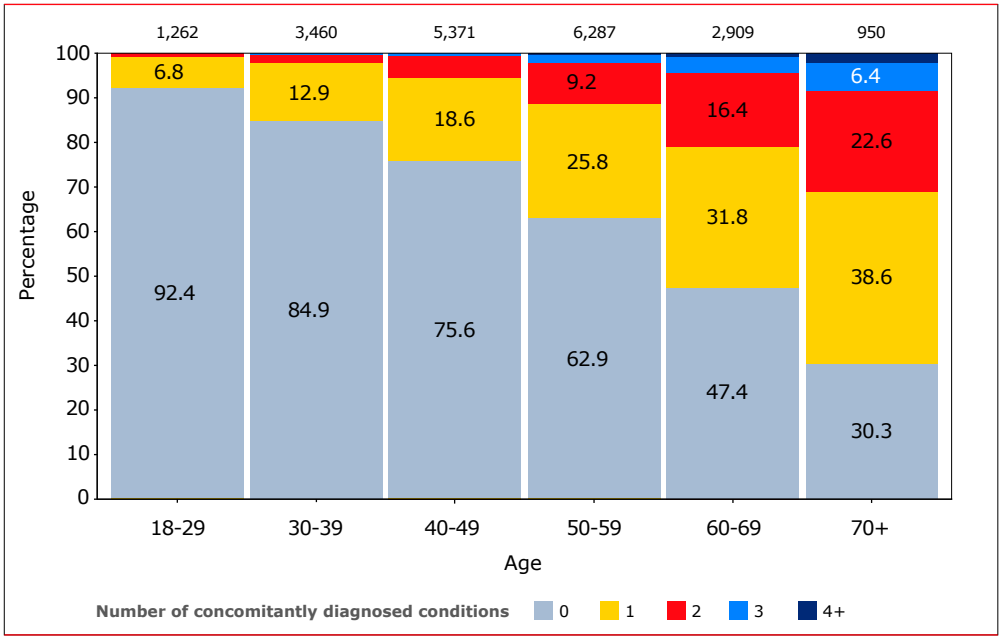
Multimorbidity

We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infection itself 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; (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 to avoid over-diagnosis of both 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.

Figure 3.13 shows the distribution of the number of concomitantly diagnosed conditions in various age categories of the adult population in 2018. The number of concomitant conditions was slightly higher in women than in men for all age categories (*Appendix Figure 3.4*). Moreover, although the average number of concomitant conditions has steadily increased over the past 10 years because of 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 3.3*, multimorbidity was independently associated with increased risk of mortality (RR 2.21 (2.11-2.31, p<0.001, per additional comorbidity diagnosed).

Figure 3.13: *Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2018. 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, commonly defined as the concomitant use of 5 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 counted 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) of the comedications. Note that co-formulated combinations, such as cotrimoxazole, have a single ATC code and therefore increase the comedication count by 1.

In 2018, 24.1% of adults in active follow up had no recorded comedication use, while 34.1%, 15.3%, 9.2%, and 5.6% used 1, 2, 3, or 4 comedications, respectively. A further 11.8% used 5 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 5 or more non-antiretroviral comedications in addition to their cART regimen. The main drivers for this increase in polypharmacy are the increasing age of the population and the increase 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, with the most pronounced differences between men and women in the youngest age groups (*Figure 3.15B*). Finally, in adults using cART in the period 2007-2018, polypharmacy was also associated with an increased risk of death (RR 2.52, 95% CI 2.24-2.85, 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 adults patients in care in 2018 are listed in *Table 3.7*.

Table 3.7: use of comedications in 2018.

Comedication use in 2018	n	%
ATC group		
Vitamins	4,142	11.0
Lipid modifying agents	3,588	9.5
Drugs for acid related disorders	3,136	8.3
Agents acting on the renin-angiotensin system	2,769	7.3
Antithrombotic agents	2,296	6.1
Psychoanaleptic drugs	1,910	5.1
Mineral supplements	1,869	4.9
Drugs used in diabetes	1,570	4.2
Beta-blocking agents	1,458	3.9
Urological drugs	1,304	3.5
Calcium channel blockers	1,149	3.0
Psycholeptic drugs	1,097	2.9
Antibacterial drugs	1,020	2.7
Sex hormones and modulators of the genital system	962	2.5
Diuretic drugs	961	2.5
Drugs for obstructive airway diseases	860	2.3
Antiepileptic drugs	743	2.0
Anti-anaemic drugs	735	1.9
Analgesic drugs	679	1.8
Antiviral drugs	637	1.7
Cardiac therapy	499	1.3
Corticosteroids (systemic)	451	1.2
Nasal preparations	409	1.1
Antimycotic drugs	368	1.0
Drugs affecting bone structure and mineralisation	306	0.8
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents	296	0.8
Thyroid therapy	292	0.8
Other nervous system drugs	255	0.7

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

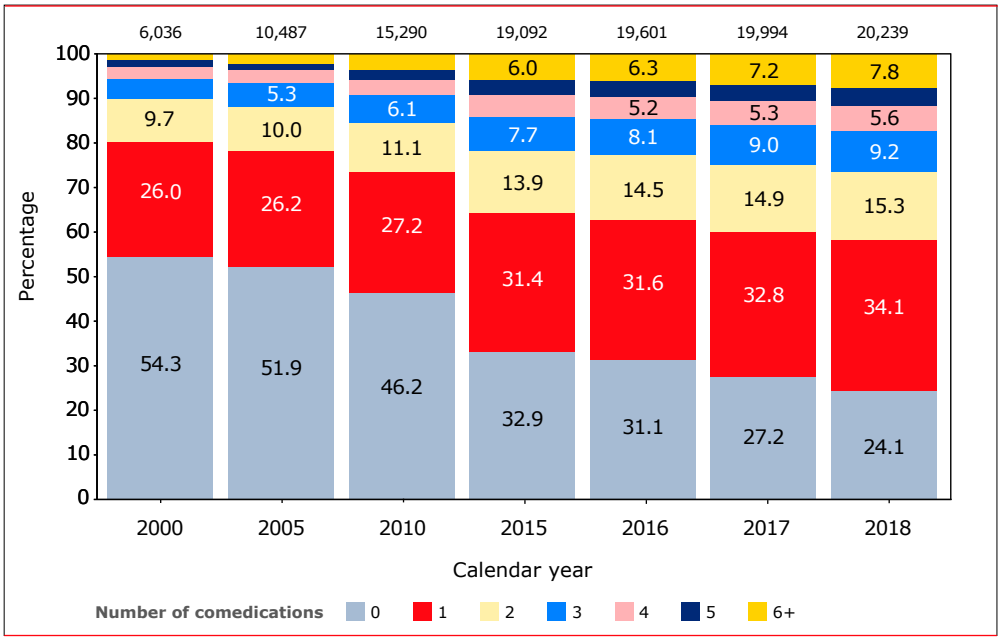
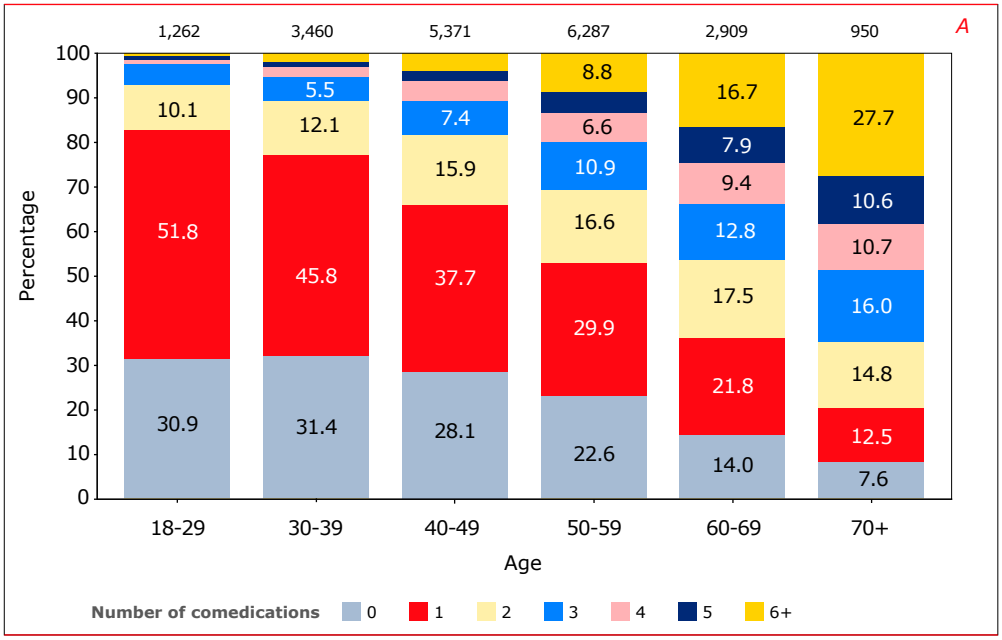


Figure 3.15: Number of comedications used by (A) age group and (B) gender. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



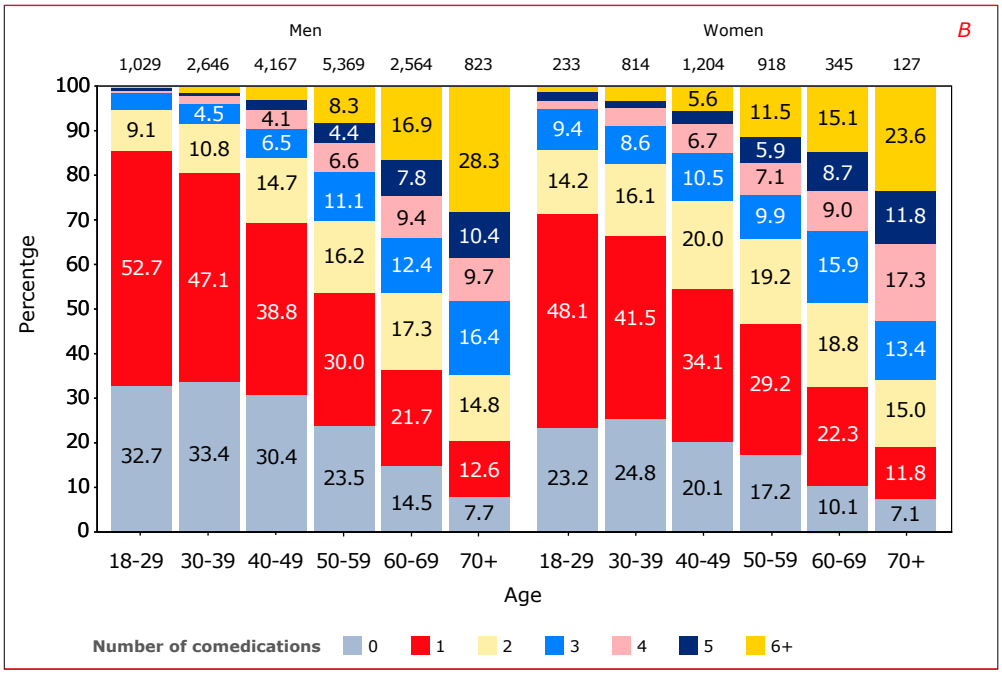
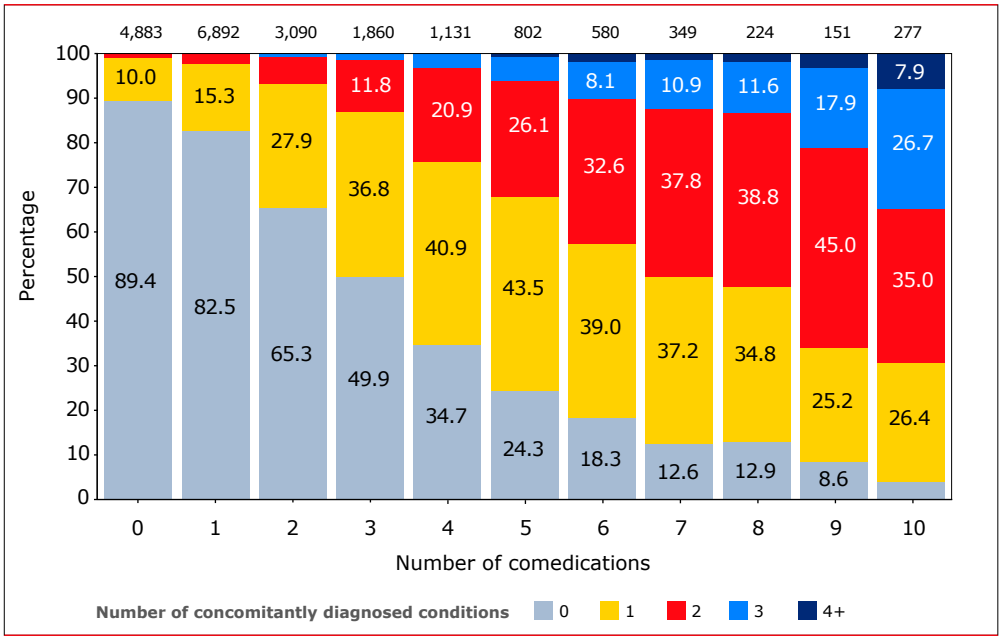


Figure 3.16: Number of comedications used by number of comorbidities diagnosed. The numbers at the top of each bar represent the number of individuals contributing data to that category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per category.



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 5-year survival 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 CVD and non-AIDS malignancies 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. The decline in age-standardised incidence in men 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. Furthermore, the declining trend of age-standardised incidence may also reflect an increasing proportion of individuals with high CD4 cell counts (partly 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, risk factors for diabetes mellitus and CVD were mainly those traditionally known to be associated with these conditions (including age, hypertension, smoking and obesity), 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 2000-2018. This suggests that cardiovascular risk management has improved over time, as illustrated by the increasing use of statins and antihypertensives over time 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 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, but not cardiovascular disease, CKD or 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.

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 older age and 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 for cardiovascular disease[52]. The increase in 'CKD' in our population in recent years

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 show 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[53,54,55,56]. 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 also reported that the effect of immunodeficiency may be stronger for infection-related non-AIDS-defining malignancies[57]. The 5-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 47.3%. Moreover, 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 0.46, 95% CI 0.27-0.80, p=0.006), independent of other traditional and HIV-related risk factors.

Multimorbidity and polypharmacy

The prevalence of non-AIDS multimorbidity is slowly increasing, driven mainly by the increasing age of the cohort, and with women experiencing more comorbidities in each age group. Multimorbidity is independently associated with increased risk of mortality (RR 2.21 (2.11-2.31), per additional comorbidity diagnosed).

Polypharmacy, defined as the concomitant use of 5 or more medications, is becoming more prevalent, mainly because of the increased age of the cohort and the associated rise in prevalence of age-associated non-AIDS comorbidities. In 2000, 3.0% of adults used 5 or more non-antiretroviral comedications alongside their cART regimen and this steadily increased to 11.8% of adults in active follow up in 2018. 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 2007-2018, polypharmacy was also associated with an increased risk of death (RR 2.52, 95% CI 2.24-2.85), independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities.

Recommendations

Although the proportion of individuals dying of AIDS in the Netherlands has markedly declined throughout the cART era, further improvement can be made by identifying individuals at earlier stages of infection, with immediate linkage to care to allow timely initiation of treatment. It is to be expected that this may also have a beneficial impact on the incidence of those comorbidities, such as non-AIDS-defining malignancies, for which advanced immunodeficiency is a contributing risk factor[58,59,60]. Indeed, our own analyses show a markedly lower risk for non-AIDS malignancies in those who initiate cART early after infection.

The relatively poor 5-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 (AGEhIV) cohort study have provided further insights into the independent contribution of HIV and HIV-associated factors, such as innate and adaptive immune and coagulation activation and inflammation. This will hopefully guide the development of interventions that target relevant pathophysiological mechanisms[9,61].

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 perhaps as yet 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 co-morbidity 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 independently associated with an increased risk of death. Adequate prevention and management of co-morbidities will become even more important as more people living with HIV are entering their 70s and 80s. Polypharmacy should also be adequately managed using of 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.

Ageing, of course, strongly contributes to the risk of developing comorbidity, ranging from cardiovascular and chronic kidney disease to diabetes mellitus and

non-AIDS malignancies. Given the steadily rising average age of individuals with HIV, it will be imperative to ensure the continued collection of high quality information regarding comorbidities and their risk factors.

Finally, 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, and the appropriate management of these risk factors offer considerable hope for lowering the comorbidity burden and ensuring healthy ageing in people living with HIV.

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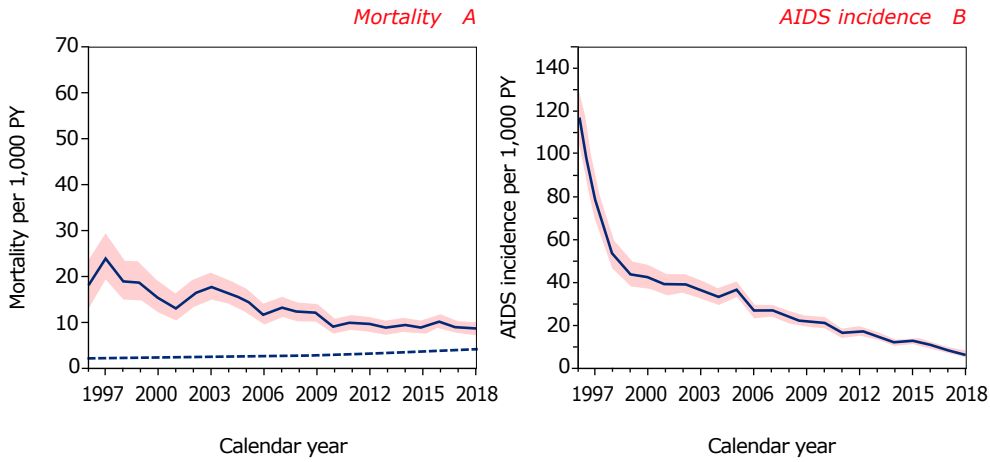
Appendix: supplementary figures and tables

Appendix Figure 3.1: *(A) Annual mortality and (B) incidence of AIDS in 26,435 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.*



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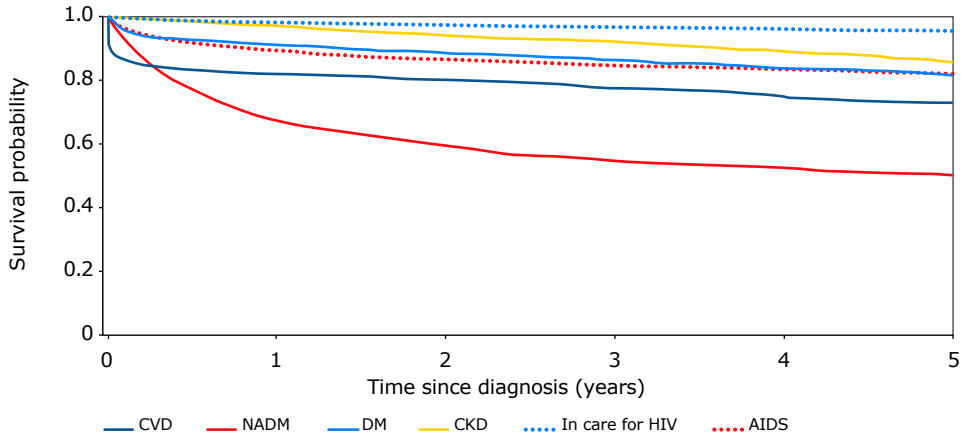
Appendix Figure 3.2: *Estimated 5-year survival following the diagnosis of cardiovascular disease, non-AIDS-defining malignancy, diabetes mellitus, chronic kidney disease. Two reference groups are included: survival from date of entry into HIV care (after 1 January 2000), and from date of first AIDS 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	1,341	1,025	902	788	675	589
NADM	1,167	740	568	447	372	307
DM	1,253	1,062	945	842	736	631
CKD	1,889	1,546	1,245	971	754	591
In care for HIV	20,593	18,603	17,295	16,076	14,885	13,687
AIDS	3,377	2,852	2,625	2,425	2,224	2,039

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

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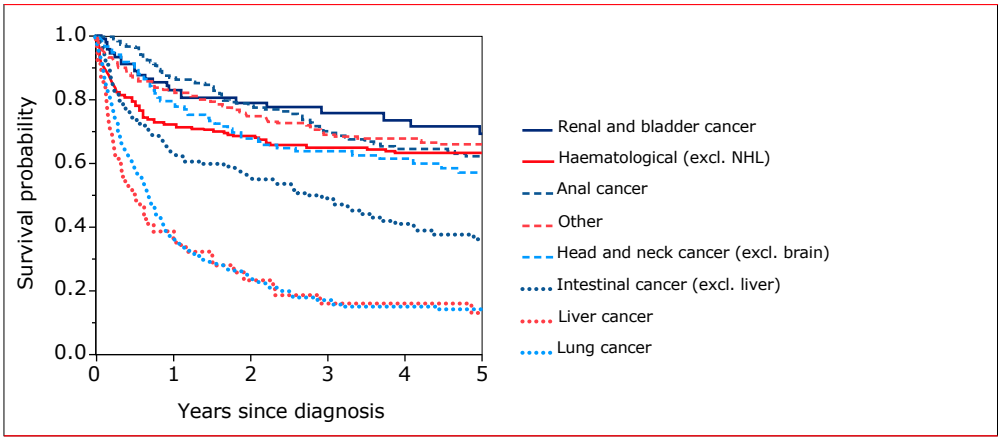
Appendix Figure 3.3: Estimated 5-year survival following the diagnosis of the most common non-AIDS-defining malignancies diagnosed between 1 January 2000 and 31 December 2018.



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

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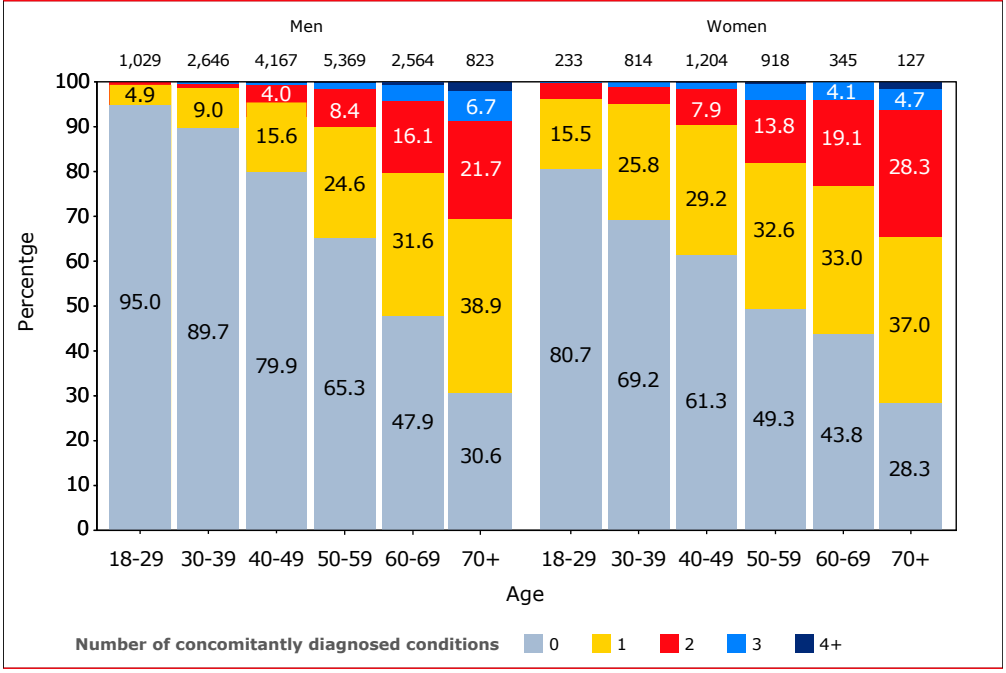
Appendix Figure 3.4: Prevalence of non-AIDS multimorbidity by gender in the adult population in 2018. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



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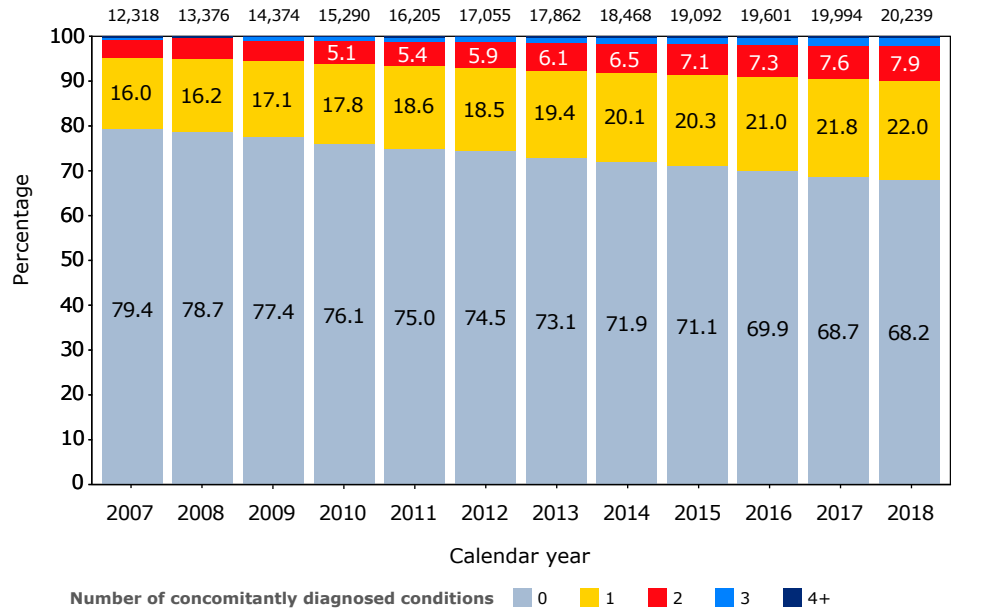
Appendix Figure 3.5: Prevalence of non-AIDS multimorbidity in the adult population. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per calendar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



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Appendix Table 3.1: Annual number of cases of death and first AIDS events among 26,435 HIV-1-positive individuals in the Netherlands recorded up to 31 December 2018.

	AIDS			Death	
Calendar year	Number of AIDS events	AIDS ≥6 weeks after diagnosis	AIDS ≥4 weeks after start of cART	Number of deaths	Number of deaths ≥6 weeks after start of cART
1996	374	234	26	51	24
1997	316	153	52	87	63
1998	250	103	42	83	69
1999	232	113	55	91	89
2000	259	101	58	85	81
2001	260	127	63	83	79
2002	308	121	66	117	79
2003	314	140	73	142	117
2004	308	142	70	144	122
2005	375	175	88	143	117
2006	296	151	77	123	99
2007	332	168	91	152	127
2008	307	158	92	153	134
2009	304	139	77	162	143
2010	313	134	85	129	116
2011	255	119	75	151	135
2012	297	139	90	156	145
2013	260	125	90	148	139
2014	212	94	64	165	151
2015	238	115	91	159	152
2016	209	97	81	190	181
2017	174	73	63	169	161
2018	111	50	39	140	136

Legend: cART=combination antiretroviral therapy.

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Appendix Table 3.2: *Absolute number of causes of death among HIV-1-positive individuals during the periods 1996-2000, 2001-2005, 2006-2010, and 2011-2018.*

Causes of death	96-00	01-05	06-10	2011	2012	2013	2014	2015	2016	2017	2018
AIDS											
AIDS - infection	69	120	147	37	16	24	18	9	6	4	3
AIDS - malignancy	60	63	61	3	13	10	5	12	8	13	8
AIDS - unclassifiable	89	63	19	2	4	.	4	6	10	3	2
Subtotal	*218*	*246*	*227*	*42*	*33*	*34*	*27*	*27*	*24*	*20*	*13*
Non-AIDS malignancies	*30*	*95*	*135*	*31*	*43*	*37*	*41*	*40*	*49*	*62*	*39*
Cardiovascular disease											
Myocardial infarction	14	30	46	12	6	5	10	7	8	4	1
Stroke	3	11	13	2	4	1	1	3	7	3	3
Other CVD	6	24	26	10	5	6	16	13	16	10	13
Subtotal	*23*	*65*	*85*	*24*	*15*	*12*	*27*	*23*	*31*	*17*	*17*
Non-AIDS infection	*23*	*42*	*32*	*3*	*6*	*6*	*7*	*5*	*7*	*3*	*10*
Liver disease	*15*	*28*	*55*	*8*	*9*	*10*	*10*	*6*	*6*	*7*	*5*
Lung disease	*7*	*11*	*30*	*6*	*4*	*8*	*5*	*15*	*13*	*14*	*6*
Non-natural death											
Accident or violence	6	11	22	2	5	3	5	1	7	2	3
Suicide	12	25	11	6	7	3	4	8	3	6	3
Euthanasia	7	5	.	1	.	1	.	.	1	.	.
Subtotal	*25*	*41*	*33*	*9*	*12*	*7*	*9*	*9*	*11*	*8*	*6*
Alcohol and substance abuse	12	15	27	2	6	5	3	2	10	4	2
Other causes	21	29	42	10	13	12	18	14	19	15	21
Unknown	23	57	53	16	15	17	18	18	20	19	21
Total	**397**	**629**	**719**	**151**	**156**	**148**	**165**	**159**	**190**	**169**	**140**

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Appendix Table 3.3: 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 (1.14-1.54)	<.001		0.93 (0.79-1.10)	0.413	
Region of birth						
Netherlands	1 (reference)		0.042	1 (reference)		0.028
Other	0.90 (0.81-1.00)	0.043		1.14 (1.01-1.29)	0.028	
HIV-1 transmission route						
Blood contact	0.72 (0.51-1.03)	0.069		0.83 (0.56-1.22)	0.334	
Heterosexual	1.05 (0.93-1.20)	0.437		0.83 (0.71-0.97)	0.018	
IDU	1.63 (1.34-1.99)	<.001		0.63 (0.48-0.82)	<.001	
MSM	1 (reference)		<.001	1 (reference)		<.001
Age*						
18-29	0.93 (0.67-1.30)	0.673	<.001	1.05 (0.85-1.29)	0.655	<.001
30-39	1 (reference)			1 (reference)		
40-49	1.54 (1.32-1.80)	<.001		1.08 (0.95-1.24)	0.228	
50-59	2.71 (2.31-3.17)	<.001		1.32 (1.14-1.54)	<.001	
60-69	4.76 (4.01-5.64)	<.001		1.37 (1.13-1.68)	0.002	
70+	10.38 (8.45-12.76)	<.001		1.75 (1.22-2.53)	0.003	
CD4 cell count**						
0-50	13.84 (11.42-16.77)	<.001	<.001	6.39 (5.12-7.99)	<.001	<.001
50-199	5.10 (4.40-5.90)	<.001		2.64 (2.23-3.14)	<.001	
200-349	2.18 (1.88-2.52)	<.001		1.56 (1.32-1.85)	<.001	
350-499	1.42 (1.22-1.65)	<.001		1.24 (1.05-1.48)	0.013	
500-749	1 (reference)			1 (reference)		
750+	0.88 (0.74-1.04)	0.138		1.09 (0.89-1.35)	0.399	
Per year longer on cART with HIV RNA >1,000 copies/ml	1.06 (1.04-1.08)	<.001	<.001	1.03 (1.01-1.06)	0.013	0.015
Treatment status at start cART						
Treatment-experienced	0.93 (0.83-1.03)	0.159		0.62 (0.55-0.71)	<.001	
Treatment-naive	1 (reference)			1 (reference)		
Prior AIDS event	1.76 (1.60-1.94)	<.001				
Hepatitis B virus positive	1.33 (1.15-1.54)	<.001		1.12 (0.92-1.36)	0.266	
Hepatitis C virus positive	1.53 (1.31-1.79)	<.001		1.35 (1.11-1.63)	0.002	

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			Death			AIDS
	RR (95% CI)	p-value	Overall p-value	RR (95% CI)	p-value	Overall p-value
Body mass index*						
<18	3.17 (2.77-3.62)	<.001	<.001			
18-25	1 (reference)					
25-30	0.66 (0.58-0.74)	<.001				
30+	0.81 (0.67-0.98)	0.034				
Smoking status						
Current smoker	1.08 (0.94-1.24)	0.293	<.001	0.75 (0.66-0.85)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	2.20 (1.93-2.50)	<.001		0.89 (0.77-1.04)	0.135	
Early cART***	0.85 (0.58-1.26)	0.430		1.13 (0.85-1.52)	0.400	

**Time-updated.*

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

****cART started within 12 months after 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 3.4: 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	46	2,614	17.6 (12.9–23.5)	2	195	10.2 (1.2–37.0)	8	183	43.7 (18.8–86.0)
050–199	190	9,266	20.5 (17.7–23.6)	10	501	20.0 (9.6–36.7)	35	1,087	32.2 (22.4–44.8)
200–349	410	20,531	20.0 (18.1–22.0)	17	1,011	16.8 (9.8–26.9)	76	1,608	47.3 (37.2–59.2)
350–499	537	37,724	14.2 (13.1–15.5)	34	1,626	20.9 (14.5–29.2)	109	3,107	35.1 (28.8–42.3)
500–749	721	82,976	8.7 (8.1–9.3)	48	3,902	12.3 (9.1–16.3)	179	6,989	25.6 (22.0–29.7)
750+	471	89,606	5.3 (4.8–5.8)	35	4,188	8.4 (5.8–11.6)	144	8,038	17.9 (15.1–21.1)

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

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	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)
	7	1,733	4.0 (1.6-8.3)	23	410	56.1 (35.6-84.2)	6	92	65.0 (23.9-141.5)
	29	5,699	5.1 (3.4-7.3)	109	1,738	62.7 (51.5-75.7)	7	242	28.9 (11.6-59.6)
	76	13,070	5.8 (4.6-7.3)	212	4,097	51.7 (45.0-59.2)	29	744	39.0 (26.1-56.0)
	121	24,459	4.9 (4.1-5.9)	254	6,871	37.0 (32.6-41.8)	19	1,660	11.4 (6.9-17.9)
	206	56,336	3.7 (3.2-4.2)	266	12,621	21.1 (18.6-23.8)	22	3,128	7.0 (4.4-10.6)
	153	63,499	2.4 (2.0-2.8)	127	10,856	11.7 (9.8-13.9)	12	3,025	4.0 (2.0-6.9)

Appendix Table 3.5: *Absolute number of first AIDS events among HIV-1-positive individuals during the periods 1996-2000, 2001-2005, 2006-2010, and 2011-2018.*

CDC event	1996-2000	2001-2005	2006-2010	2011-2015	2016-2018	Total	
	n	n	n	n	n	n	%
AIDS dementia complex / HIV encephalopathy	37	47	51	44	13	192	3.05
Bacterial pneumonia, recurrent	48	63	65	76	50	302	4.80
CMV ≥13 years	27	35	29	34	3	128	2.03
CMV colitis/proctitis	1	.	.	.	3	4	0.06
CMV meningo-encephalitis	.	.	.	.	1	1	0.02
CMV pneumonitis	.	.	.	.	4	4	0.06
CMV retinitis	30	20	12	11	7	80	1.27
Candidiasis trachea, bronchi, lungs	7	13	7	6	3	36	0.57
Candidiasis oesophageal	258	236	251	221	79	1,045	16.60
Cervical cancer	3	4	6	5	3	21	0.33
Coccidioidomycosis, disseminated or extrapulmonary	.	.	1	.	.	1	0.02
Cryptococcosis, disseminated or extrapulmonary	21	31	33	11	9	105	1.67
Cryptosporidiosis	22	12	10	12	2	58	0.92
Cystoisosporiasis	3	9	6	.	.	18	0.29
Wasting syndrome due to HIV	48	57	77	76	37	295	4.68
Herpes simplex virus, chronic ulcer	.	1	.	3	5	9	0.14
Herpes simplex virus	32	41	60	37	9	179	2.84
Histoplasmosis, disseminated or extrapulmonary	9	12	10	7	1	39	0.62
Kaposi's sarcoma	153	151	186	137	39	666	10.58
Leishmaniasis, visceral	.	1	2	2	2	7	0.11
Microsporidiosis	11	1	3	1	.	16	0.25
Mycobacterium, other species/unidentified (disseminated/extrapulmonary)	20	13	7	10	3	53	0.84
Mycobacterium, other species/unidentified (pulmonary)	.	3	4	10	3	20	0.32
Mycobacterium avium/kansasii (disseminated/ extrapulmonary)	25	19	28	9	6	87	1.38
Mycobacterium avium/kansasii (pulmonary)	.	1	.	.	4	5	0.08
Non-Hodgkin's lymphoma (NHL), AIDS-defining	59	86	81	94	32	352	5.59
Penicilliosis	.	.	1	.	.	1	0.02
Pneumocystis jirovecii extrapulmonary	1	1	3	.	.	5	0.08
Pneumocystis jirovecii pulmonary	335	297	326	263	117	1,338	21.25
Primary central nervous system lymphoma	8	5	9	7	4	33	0.52
Progressive multifocal leucoencephalopathy	18	25	35	23	3	104	1.65

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CDC event	1996-2000	2001-2005	2006-2010	2011-2015	2016-2018	Total	
	n	n	n	n	n	n	%
Salmonella septicaemia, recurrent	2	.	.	.	.	2	0.03
Toxoplasmosis of the brain	70	97	55	42	17	281	4.46
Tuberculosis, extrapulmonary/disseminated	78	110	81	51	9	329	5.22
Tuberculosis, pulmonary	103	172	113	67	26	481	7.64
Total	**1,429**	**1,563**	**1,552**	**1,259**	**494**	**6,297**	**100.00**

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

Appendix Table 3.6A: Incidence of diabetes mellitus from 2000 onwards according to gender and age.

	Men			Women		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	6	12,055	0.5 (0.2-1.1)	25	6,515	3.8 (2.5-5.7)
30-39	85	41,457	2.1 (1.6-2.5)	78	15,707	5.0 (3.9-6.2)
40-49	280	67,825	4.1 (3.7-4.6)	99	14,971	6.6 (5.4-8.1)
50-59	330	49,565	6.7 (6.0-7.4)	62	6,966	8.9 (6.8-11.4)
60-69	204	18,648	10.9 (9.5-12.5)	20	2,373	8.4 (5.1-13.0)
70+	44	4,182	10.5 (7.6-14.1)	5	710	7.0 (2.3-16.4)

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

Appendix Table 3.6B: Incidence of cardiovascular disease (myocardial infarction, stroke, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy) from 2000 onwards according to gender and age.

	Men			Women		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	6	12,051	0.5 (0.2-1.1)	6	6,577	0.9 (0.3-2.0)
30-39	59	41,561	1.4 (1.1-1.8)	22	16,002	1.4 (0.9-2.1)
40-49	293	68,090	4.3 (3.8-4.8)	57	15,367	3.7 (2.8-4.8)
50-59	457	49,345	9.3 (8.4-10.2)	29	7,268	4.0 (2.7-5.7)
60-69	289	18,234	15.8 (14.1-17.8)	22	2,415	9.1 (5.7-13.8)
70+	91	3,949	23.0 (18.6-28.3)	7	694	10.1 (4.1-20.8)

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

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Appendix Table 3.6C: Incidence of chronic kidney disease (an estimated glomerular filtration rate below 60 ml/min, estimated with the Cockcroft-Gault equation, and confirmed after 6 months or more) from 2008 onwards, according to gender and age.

	Men			Women		
Age	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**
18-29	4	8,930	0.4 (0.1-1.1)	4	3,539	1.1 (0.3-2.9)
30-39	39	25,952	1.5 (1.1-2.1)	10	9,908	1.0 (0.5-1.9)
40-49	179	47,323	3.8 (3.2-4.4)	57	11,526	4.9 (3.7-6.4)
50-59	433	39,729	10.9 (9.9-12.0)	113	5,856	19.3 (15.9-23.2)
60-69	506	15,333	33.0 (30.2-36.0)	93	1,790	52.0 (41.9-63.6)
70+	212	2,893	73.3 (63.7-83.8)	32	385	83.1 (56.8-117.2)

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

Appendix Table 3.6D: Incidence of non-AIDS-defining malignancy (including Castleman's disease, but excluding precancerous stages of anal and cervical cancer, basal-cell carcinoma, and squamous-cell carcinoma of the skin) from 2000 onwards, according to gender and age.

	Men			Women		
Age	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**
18-29	11	12,044	0.9 (0.5-1.6)	4	6,593	0.6 (0.2-1.6)
30-39	67	41,501	1.6 (1.3-2.1)	20	16,016	1.2 (0.8-1.9)
40-49	230	68,475	3.4 (2.9-3.8)	57	15,454	3.7 (2.8-4.8)
50-59	340	50,567	6.7 (6.0-7.5)	49	7,274	6.7 (5.0-8.9)
60-69	261	19,264	13.5 (12.0-15.3)	16	2,449	6.5 (3.7-10.6)
70+	99	4,152	23.8 (19.4-29.0)	9	727	12.4 (5.7-23.5)

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

Appendix Table 3.6E: Incidence of myocardial infarction from 2000 onwards, according to gender and age.

	Men			Women		
Age	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**
18-29	1	12,067	0.1 (0.0-0.5)	2	6,599	0.3 (0.0-1.1)
30-39	27	41,649	0.6 (0.4-0.9)	6	16,049	0.4 (0.1-0.8)
40-49	185	68,477	2.7 (2.3-3.1)	25	15,519	1.6 (1.0-2.4)
50-59	247	50,327	4.9 (4.3-5.6)	17	7,376	2.3 (1.3-3.7)
60-69	164	19,147	8.6 (7.3-10.0)	9	2,479	3.6 (1.7-6.9)
70+	33	4,361	7.6 (5.2-10.6)	1	750	1.3 (0.0-7.4)

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

Appendix Table 3.6F: Incidence of stroke from 2000 onwards, according to gender and age.

	Men			Women		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	5	12,051	0.4 (0.1-1.0)	3	6,584	0.5 (0.1-1.3)
30-39	31	41,624	0.7 (0.5-1.1)	16	16,018	1.0 (0.6-1.6)
40-49	92	68,798	1.3 (1.1-1.6)	31	15,484	2.0 (1.4-2.8)
50-59	145	50,947	2.8 (2.4-3.3)	11	7,375	1.5 (0.7-2.7)
60-69	106	19,601	5.4 (4.4-6.5)	11	2,475	4.4 (2.2-8.0)
70+	46	4,423	10.4 (7.6-13.9)	6	738	8.1 (3.0-17.7)

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

Appendix Table 3.6G: Incidence of anal cancer in men from 2000 onwards, according to age.

	Men		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	0	12,067	0.0 (0.0.-0.3)
30-39	11	41,693	0.3 (0.1-0.5)
40-49	57	68,916	0.8 (0.6-1 .1)
50-59	77	51,217	1.5 (1.2-1.9)
60-69	24	20,008	1.2 (0.8-1.8)
70+	3	4,664	0.6 (0.1-1.9)

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

Appendix Table 3.6H: Incidence of non-AIDS-defining disease (first occurrence of cardiovascular disease, diabetes mellitus, or non-AIDS-defining malignancy) from 2000 onwards, according to gender and age.

	Men			Women		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	22	12,016	1.8 (1.1-2.8)	33	6,480	5.1 (3.5-7.2)
30-39	200	41,117	4.9 (4.2-5.6)	112	15,605	7.2 (5.9-8.6)
40-49	742	66,229	11.2 (10.4-12.0)	197	14,578	13.5 (11.7-15.5)
50-59	999	46,497	21.5 (20.2-22.9)	126	6,627	19.0 (15.8-22.6)
60-69	601	16,239	37.0 (34.1-40.1)	48	2,207	21.7 (16.0-28.8)
70+	178	3,173	56.1 (48.2-65.0)	16	587	27.3 (15.6-44.3)

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

Appendix Table 3.7: 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	1.22 (1.08-1.36)	<.001	.	1.68 (1.37-2.06)	<.001	.
Region of birth						
Netherlands	1 (reference)	.	0.649	1 (reference)	.	0.012
Other	1.02 (0.94-1.10)	0.649	.	0.85 (0.74-0.97)	0.013	.
HIV-1 transmission route						
MSM	1 (reference)	.	<.001	1 (reference)	.	<.001
Heterosexual	1.26 (1.14-1.39)	<.001	.	1.31 (1.13-1.52)	<.001	.
IDU	1.38 (1.12-1.70)	0.002	.	1.31 (0.95-1.82)	0.103	.
Blood contact	1.32 (1.02-1.72)	0.035	.	1.31 (0.87-1.97)	0.188	.
Age*						
18-29	0.58 (0.43-0.78)	<.001	<.001	0.47 (0.25-0.90)	0.022	<.001
30-39	1 (reference)	.	.	1 (reference)	.	.
40-49	2.04 (1.79-2.33)	<.001	.	2.70 (2.11-3.46)	<.001	.
50-59	3.74 (3.28-4.28)	<.001	.	5.61 (4.39-7.18)	<.001	.
60-69	6.35 (5.48-7.35)	<.001	.	9.73 (7.49-12.64)	<.001	.
70+	9.41 (7.75-11.44)	<.001	.	14.35 (10.45-19.70)	<.001	.
CD4 cell count**						
<50	4.08 (3.18-5.24)	<.001	<.001	3.10 (1.99-4.82)	<.001	<.001
50-199	1.84 (1.57-2.16)	<.001	.	1.54 (1.19-2.01)	0.001	.
200-349	1.27 (1.13-1.43	<.001	.	1.32 (1.10-1.59)	0.003	.
350-499	1.07 (0.97-1.19)	0.183	.	1.14 (0.97-1.34)	0.120	.
500-749	1 (reference)	.	.	1 (reference)	.	.
750+	1.16 (1.05-1.28)	0.003	.	1.35 (1.16-1.57)	<.001	.
Per year longer with CD4 <200 cells/mm^3	.	0.215	.	1.01 (0.97-1.05)	0.613	.
Prior AIDS event	1.25 (1.15-1.35)	<.001	.	1.14 (1.01-1.29)	0.040	.
Per year longer on cART while HIV RNA>1000 copies/ml	1.03 (1.00-1.05)	0.017	.	1.03 (0.99-1.06)	0.125	.
Treatment status						
Not (yet) started cART	1.19 (1.04-1.36)	0.012	<.001	0.98 (0.77-1.25)	0.875	0.021
Treatment-experienced at start cART	1.33 (1.21-1.47)	<.001	.	1.24 (1.07-1.45)	0.005	.
Treatment-naive at start	1 (reference)	.	.	1 (reference)	.	.
Per year longer on cART	1.01 (1.00-1.01)	0.228	.	1.00 (0.99-1.01)	0.900	.
Early cART within 12 months after last HIV-negative	0.89 (0.70-1.14)	0.352	.	1.16 (0.82-1.63)	0.404	.

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	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
	1.05 (0.85–1.29)	0.653	.	1.19 (1.01–1.42)	0.042	.	0.62 (0.53–0.74)	<.001	.
	1 (reference)	.	0.019	1 (reference)	.	<.001	1 (reference)	.	<.001
	0.84 (0.73–0.97)	0.020	.	1.42 (1.25–1.62)	<.001	.	0.78 (0.70–0.88)	<.001	.
	1 (reference)	.	0.026	1 (reference)	.	<.001	1 (reference)	.	0.073
	0.99 (0.83–1.17)	0.886	.	1.54 (1.32–1.81)	<.001	.	1.00 (0.86–1.16)	0.998	.
	1.48 (1.07–2.06)	0.018	.	1.61 (1.13–2.30)	0.008	.	1.41 (1.04–1.90)	0.026	.
	1.65 (1.13–2.42)	0.010	.	1.64 (1.11–2.44)	0.014	.	1.33 (0.94–1.89)	0.112	.
	0.69 (0.41–1.17)	0.173	<.001	0.60 (0.40–0.89)	0.012	<.001	0.34 (0.15–0.81)	0.015	<.001
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	2.25 (1.75–2.89)	<.001	.	1.55 (1.28–1.88)	<.001	.	2.98 (2.18–4.07)	<.001	.
	4.33 (3.37–5.56)	<.001	.	2.40 (1.97–2.93)	<.001	.	8.18 (6.06–11.05)	<.001	.
	8.31 (6.38–10.83)	<.001	.	4.08 (3.26–5.10)	<.001	.	23.03 (17.01–31.17)	<.001	.
	14.70 (10.74–20.12)	<.001	.	4.06 (2.87–5.75)	<.001	.	45.09 (32.63–62.31)	<.001	.
	3.05 (1.86–5.00)	<.001	<.001	6.11 (4.29–8.70)	<.001	<.001	1.67 (0.88–3.17)	0.015	0.004
	2.06 (1.58–2.69)	<.001	.	1.95 (1.51–2.52)	<.001	.	1.61 (1.25–2.07)	<.001	.
	1.39 (1.15–1.69)	<.001	.	1.09 (0.90–1.33)	0.383	.	1.13 (0.95–1.34)	0.166	.
	1.09 (0.92–1.29)	0.332	.	0.97 (0.82–1.15)	0.740	.	1.02 (0.89–1.17)	0.810	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	0.97 (0.82–1.14)	0.682	.	1.16 (0.99–1.36)	0.059	.	0.93 (0.82–1.06)	0.267	.
	0.97 (0.93–1.00)	0.081	.	0.98 (0.94–1.02)	0.243	.	0.98 (0.95–1.02)	0.309	.
	1.27 (1.11–1.45)	<.001	.	1.34 (1.18–1.53)	<.001	.	1.14 (1.02–1.27)	0.018	.
	1.00 (0.97–1.04)	0.822	.	1.02 (0.98–1.05)	0.370	.	0.98 (0.95–1.01)	0.266	.
	1.28 (1.02–1.62)	0.035	0.007	1.42 (1.15–1.77)	0.001	<.001	0.41 (0.28–0.59)	<.001	<.001
	1.23 (1.04–1.46)	0.015	.	1.29 (1.08–1.54)	0.005	.	1.15 (0.99–1.34)	0.067	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	1.00 (0.99–1.02)	0.609	.	1.00 (0.99–1.02)	0.846	.	0.99 (0.98–1.00)	0.101	.
	0.46 (0.27–0.80)	0.006	.	0.92 (0.59–1.42)	0.694	.	0.94 (0.72–1.24)	0.676	.

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value
Body mass index*						
0-18	1.44 (1.17-1.78)	<.001	<.001	1.10 (0.78-1.56)	0.578	0.172
18-25	1 (reference)	.	.	1 (reference)	.	.
25-30	1.20 (1.10-1.31)	<.001	.	0.99 (0.86-1.13)	0.862	.
30+	1.88 (1.67-2.12)	<.001	.	1.05 (0.84-1.31)	0.650	.
Hepatitis B virus positive	1.17 (1.03-1.34)	0.019	.	1.02 (0.82-1.28)	0.832	.
Hepatitis C virus positive	1.04 (0.91-1.19)	0.542	.	0.99 (0.80-1.22)	0.918	.
Hypertension	1.14 (1.05-1.22)	<.001	.	1.19 (1.06-1.33)	0.004	.
Smoking status						
Current smoker	1.37 (1.25-1.50)	<.001	<.001	1.86 (1.61-2.15)	<.001	<.001
Never smoker	1 (reference)	.	.	1 (reference)	.	.
Past smoker	1.45 (1.32-1.60)	<.001	.	1.58 (1.35-1.85)	<.001	.
Calendar year period						
2000-2005	1.19 (1.06-1.33)	0.004	<.001	1.45 (1.21-1.74)	<.001	<.001
2006-2010	1.23 (1.13-1.35)	<.001	.	1.27 (1.10-1.47)	0.001	.
2011-2018	1 (reference)	.	.	1 (reference)	.	.
Recent use of ABC***		.	.	1.56 (1.38-1.77)	<.001	.
Per year longer on LOP/r		.	.	1.01 (0.99-1.03)	0.198	.
Per year longer on IDV		.	.	1.00 (0.99-1.01)	0.821	.
Per year longer on ZDV		.	.		.	.
Per year longer on d4T		.	.		.	.
Per year longer on ddI		.	.		.	.
Per year longer on TAF		.	.		.	.
Per year longer on TDF		.	.		.	.
Prior cardiovascular event		.	.		.	.
Prior diabetes		.	.		.	.
Current use of cobicistat		.	.		.	.
Current use of dolutegravir		.	.		.	.
Current use of rilpivirine		.	.		.	.
Current use of bictegravir		.	.		.	.

**Time-updated.*

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

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

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

	Non-AIDS-defining malignancy			Diabetes mellitus			CKD		
	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value
	1.99 (1.50–2.64)	<.001	<.001	1.34 (0.90–2.00)	0.152	<.001	1.59 (1.18–2.13)	0.002	0.021
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	0.83 (0.71–0.97)	0.017	.	2.17 (1.87–2.51)	<.001	.	1.09 (0.97–1.23)	0.138	.
	0.98 (0.77–1.25)	0.890	.	4.55 (3.83–5.41)	<.001	.	1.15 (0.97–1.37)	0.115	.
	1.64 (1.35–2.00)	<.001	.	1.08 (0.86–1.36)	0.498	.	1.45 (1.20–1.74)	<.001	.
	1.05 (0.84–1.31)	0.683	.	1.05 (0.83–1.32)	0.702	.	1.40 (1.19–1.65)	<.001	.
	0.94 (0.82–1.07)	0.333	.	1.19 (1.06–1.35)	0.004	.	1.13 (1.02–1.25)	0.019	.
	1.44 (1.23–1.69)	<.001	<.001	0.97 (0.84–1.13)	0.718	<.001	0.85 (0.75–0.96)	0.008	<.001
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	1.73 (1.47–2.04)	<.001	.	1.27 (1.08–1.48)	0.003	.	0.98 (0.87–1.11)	0.720	.
	0.88 (0.71–1.08)	0.212	0.021	1.19 (0.98–1.44)	0.082	0.091		.	.
	1.15 (0.98–1.33)	0.078	.	1.17 (1.00–1.36)	0.046	.	1.06 (0.92–1.23)	0.421	0.423
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.	1.01 (1.00–1.02)	0.092	.		.	.
		.	.	1.03 (1.00–1.06)	0.063	.		.	.
		.	.	1.06 (1.03–1.10)	<.001	.		.	.
		.	.		.	.	1.09 (0.94–1.27)	0.264	.
		.	.		.	.	1.01 (1.00–1.01)	0.245	.
		.	.		.	.	1.60 (1.35–1.89)	<.001	.
		.	.		.	.	1.37 (1.15–1.64)	<.001	.
		.	.		.	.	1.59 (1.34–1.89)	<.001	.
		.	.		.	.	3.36 (2.99–3.78)	<.001	.
		.	.		.	.	1.44 (1.18–1.76)	<.001	<.001
		.	.		.	.	10.26 (2.55–41.33)	0.001	0.017

Appendix Table 3.8: *Specific CDC-B and CDC-C (AIDS) events occurring in individuals on cART with undetectable viral load between 2000 and 2018.*

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Aspergillosis, invasive pulmonary	2	0.1%	0	0.0%
	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis oropharyngeal ≥13 years	681	21.8%	57	25.2%
	Candidiasis vulvovaginal, recurrent/ persistent	54	1.7%	1	0.4%
	Cardiomyopathy, HIV-related	3	0.1%	0	0.0%
	Cardiomyopathy, with HIV component	10	0.3%	1	0.4%
	Cervical dysplasia	538	17.2%	9	4.0%
	Diarrhoea, HIV-related ≥30 days	64	2.1%	1	0.4%
	Herpes zoster, multidermatomal	7	0.2%	0	0.0%
	Herpes zoster, recurrent/ unspecified multidermatomal	218	7.0%	10	4.4%
	Herpes zoster, recurrent unidermatomal	1	0.0%	1	0.4%
	HIV-associated nephropathy	20	0.6%	2	0.9%
	Fever of unknown origin / HIV-related fever	6	0.2%	0	0.0%
	Myelopathy, HIV-related	10	0.3%	0	0.0%
	Neuropathy, HIV-related	87	2.8%	2	0.9%
	Neuropathy, with HIV component	41	1.3%	1	0.4%
	Nocardiosis	1	0.0%	1	0.4%
	Oral hairy leucoplakia	51	1.6%	1	0.4%
	Pelvic inflammatory disease	4	0.1%	0	0.0%
	Thrombocytopenia, ≥13 years, HIV-related	94	3.0%	2	0.9%
	Thrombocytopenia, ≥13 years, with HIV component	6	0.2%	1	0.4%
	Weight loss (>10%) HIV-related or unknown origin	38	1.2%	2	0.9%
Subtotal		**1,937**	**62.1%**	**92**	**40.7%**
CDC-C events	AIDS dementia complex – HIV encephalopathy	45	1.4%	4	1.8%
	Bacterial pneumonia, recurrent	282	9.0%	15	6.6%
	CMV ≥13 years	19	0.6%	4	1.8%
	CMV oesophagitis	1	0.0%	1	0.4%
	CMV retinitis	15	0.5%	2	0.9%
	Candidiasis trachea, bronchi, lungs	9	0.3%	2	0.9%
	Candidiasis, esophageal	212	6.8%	24	10.6%
	Cervical cancer	8	0.3%	1	0.4%
	Coccidioidomycosis, disseminated/extrapulmonary	1	0.0%	0	0.0%

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CD4 category									
50–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
1	0.2%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
170	29.4%	140	20.1%	116	19.2%	124	18.9%	74	20.5%
5	0.9%	10	1.4%	17	2.8%	15	2.3%	6	1.7%
0	0.0%	0	0.0%	2	0.3%	0	0.0%	1	0.3%
3	0.5%	1	0.1%	2	0.3%	2	0.3%	1	0.3%
56	9.7%	121	17.4%	121	20.0%	144	22.0%	87	24.1%
6	1.0%	16	2.3%	11	1.8%	22	3.4%	8	2.2%
0	0.0%	2	0.3%	2	0.3%	1	0.2%	2	0.6%
24	4.2%	52	7.5%	45	7.5%	56	8.5%	31	8.6%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
3	0.5%	3	0.4%	4	0.7%	4	0.6%	4	1.1%
1	0.2%	2	0.3%	0	0.0%	1	0.2%	2	0.6%
4	0.7%	2	0.3%	0	0.0%	1	0.2%	3	0.8%
8	1.4%	16	2.3%	24	4.0%	22	3.4%	15	4.2%
7	1.2%	8	1.2%	9	1.5%	10	1.5%	6	1.7%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
14	2.4%	11	1.6%	8	1.3%	9	1.4%	8	2.2%
0	0.0%	1	0.1%	0	0.0%	2	0.3%	1	0.3%
20	3.5%	20	2.9%	20	3.3%	21	3.2%	11	3.0%
1	0.2%	3	0.4%	0	0.0%	1	0.2%	0	0.0%
5	0.9%	9	1.3%	7	1.2%	9	1.4%	6	1.7%
329	**56.9%**	**417**	**60.0%**	**388**	**64.2%**	**445**	**67.9%**	**266**	**73.7%**
8	1.4%	10	1.4%	8	1.3%	8	1.2%	7	1.9%
49	8.5%	76	10.9%	61	10.1%	59	9.0%	22	6.1%
4	0.7%	3	0.4%	5	0.8%	1	0.2%	2	0.6%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
5	0.9%	2	0.3%	5	0.8%	1	0.2%	0	0.0%
1	0.2%	4	0.6%	0	0.0%	1	0.2%	1	0.3%
51	8.8%	50	7.2%	35	5.8%	30	4.6%	22	6.1%
1	0.2%	2	0.3%	1	0.2%	3	0.5%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
	Cryptococcosis extrapulmonary	16	0.5%	6	2.7%
	Cryptosporidiosis	10	0.3%	4	1.8%
	Cystoisosporiasis	1	0.0%	0	0.0%
	HIV wasting	16	0.5%	7	3.1%
	Herpes simplex virus, chronic ulcer	8	0.3%	0	0.0%
	Herpes simplex virus	62	2.0%	7	3.1%
	Histoplasmosis, disseminated or extrapulmonary	4	0.1%	3	1.3%
	Kaposi sarcoma	93	3.0%	5	2.2%
	Leishmaniasis, visceral	5	0.2%	1	0.4%
	Microsporidiosis	5	0.2%	2	0.9%
	Mycobacterium, other/unidentified (disseminated/extrapulmonary)	6	0.2%	1	0.4%
	Mycobacterium, other/unidentified (pulmonary)	5	0.2%	0	0.0%
	Mycobacterium avium / M. kansasii, disseminated/extrapulmonary	20	0.6%	5	2.2%
	Mycobacterium avium/kansasii, pulmonary	3	0.1%	0	0.0%
	non-Hodgkin's lymphoma, AIDS-defining	127	4.1%	7	3.1%
	Pneumocystis jirovecii, extrapulmonary	1	0.0%	0	0.0%
	Pneumocystis jirovecii, pulmonary	64	2.1%	16	7.1%
	Primary central nervous system lymphoma	5	0.2%	0	0.0%
	Progressive multifocal leucoencephalopathy	18	0.6%	4	1.8%
	Toxoplasmosis of the brain	17	0.5%	8	3.5%
	Tuberculosis, extrapulmonary/disseminated	36	1.2%	2	0.9%
	Tuberculosis, pulmonary	68	2.2%	3	1.3%
Subtotal		**1,182**	**37.9%**	**134**	**59.3%**
Total		**3,119**	**100.0%**	**226**	**100.0%**

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

CD4 category										
50–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
5	0.9%	3	0.4%	1	0.2%	1	0.2%	0	0.0%
0	0.0%	1	0.1%	3	0.5%	1	0.2%	1	0.3%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
5	0.9%	1	0.1%	2	0.3%	1	0.2%	0	0.0%
0	0.0%	0	0.0%	1	0.2%	5	0.8%	2	0.6%
6	1.0%	13	1.9%	16	2.6%	16	2.4%	4	1.1%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
10	1.7%	24	3.5%	21	3.5%	22	3.4%	11	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%
1	0.2%	3	0.4%	0	0.0%	1	0.2%	0	0.0%
2	0.3%	0	0.0%	2	0.3%	1	0.2%	0	0.0%
7	1.2%	4	0.6%	2	0.3%	1	0.2%	1	0.3%
0	0.0%	1	0.1%	0	0.0%	1	0.2%	1	0.3%
32	5.5%	33	4.7%	24	4.0%	24	3.7%	7	1.9%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
24	4.2%	10	1.4%	7	1.2%	6	0.9%	1	0.3%
1	0.2%	2	0.3%	1	0.2%	1	0.2%	0	0.0%
6	1.0%	4	0.6%	2	0.3%	2	0.3%	0	0.0%
3	0.5%	4	0.6%	1	0.2%	1	0.2%	0	0.0%
8	1.4%	7	1.0%	4	0.7%	10	1.5%	5	1.4%
15	2.6%	19	2.7%	14	2.3%	11	1.7%	6	1.7%
249	**43.1%**	**278**	**40.0%**	**216**	**35.8%**	**210**	**32.1%**	**95**	**26.3%**
578	**100.0%**	**695**	**100.0%**	**604**	**100.0%**	**655**	**100.0%**	**361**	**100.0%**