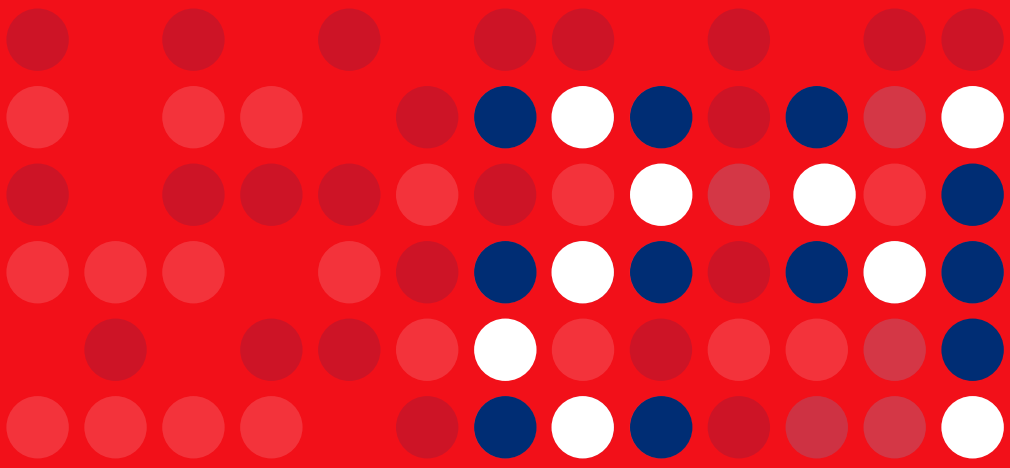
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2024

Chapter 5: Morbidity and mortality



5. Morbidity and mortality

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Summary

AIDS, mortality and causes of death

AIDS-related deaths have decreased dramatically since ART became available in the Netherlands in 1996. The limited number of deaths from AIDS each year mainly occur among those who present late for care with already advanced immunodeficiency. Death is increasingly more likely to be the result of a non-AIDS cause, with non-AIDS malignancies and CVD being the most common. This not only reflects the increased risk of non-AIDS morbidity in individuals with more advanced HIV infection, but also the continuously increasing age of the population of individuals in care. As a result, on average, the mortality rate among people with HIV in the Netherlands remains substantially higher than in the general Dutch population. In the late 1990s and 2000s, the excess mortality was high but was quickly decreasing over time. Several studies have even found that mortality rates in individuals on ART who achieve CD4 cell counts above 500 cells/mm^3, may even drop below general population rates[1,2]. However, in the total population of people with HIV in the Netherlands the rate of decline of the observed excess mortality is slowing down over the years. The ratio of the observed mortality among PWH compared to the age/sex-adjusted mortality observed in the general population, decreased from 9.94 in 1996, to 6.54 in 2000, to 5.83 in 2005, to 3.03 in 2010, to 2.33 in 2015 and has remained constant at around 2.0 since 2017. In 2023 the ratio was 2.01 times the observed age- and sex-standardized mortality in the general population of the Netherlands. In all investigated sub groups, the ratio of the observed over expected mortality declined over time but at the end of follow-up in 2023 remained substantially higher than one. The native Dutch, men who have sex with men, and those with higher pre-ART nadir CD4 counts had the lowest excess mortality.

In 2021, for the first time there was a substantial increase in the absolute mortality rate in people with HIV in the Netherlands during the period 2019 to 2021; from 8.46 deaths per 1000 person years in 2019, to 9.14 in 2020 and 10.77 in 2021. The slightly increased mortality rates in 2020 and 2021 appear mostly driven by an increase in the number of non-AIDS infectious causes of death, which include COVID-19-related deaths. Even though the observed mortality rate increased in 2020 and 2021, the ratio of the observed over expected mortality remained stable because this increase in mortality in people with HIV coincides with – and is

proportional to – the excess mortality of ca. 10% that was observed in the general Dutch population in 2020 and 2021 (as well as in other Western countries) because of COVID-19-related deaths and other indirect adverse health effects of the COVID-19 epidemic in the Netherlands[3]. In 2022 the observed mortality rate of 9.79 deaths per 1,000 person years had not completely returned to pre-COVID-19 levels. And in 2023 the observed mortality rate had again increased, to 11.46 deaths per 1,000 person years. However, in 2022 and 2023 the ratio of the observed over the expected age/sex-adjusted mortality remained stable, suggesting the slight increase in the mortality rate is driven by the continued ageing of the population of people with HIV and perhaps also other general factors in the Netherlands.

Cardiovascular disease and diabetes

Whereas the crude incidence of CVD and diabetes mellitus in men and women was found to have remained relatively stable, the age-standardised incidence for CVD declined over time in men and women, while the age-adjusted incidence for diabetes mellitus only declined in men and in fact increased slightly over time for women. When comparing the age- and sex-stratified prevalence of diabetes mellitus in the population of people with HIV with that observed in the general Dutch population, we observed that in men the prevalence of diabetes was lower in all age strata, while in women aged 20 up to 69 year old the observed prevalence of diabetes was higher compared to the prevalence in the general population. The age- and sex-stratified prevalence of coronary artery disease (myocardial infarction, angina pectoris) in both men and women with HIV was fairly equal compared to the reference prevalence in the general population. However, we cannot exclude the possibility that people with HIV who develop coronary artery disease have poorer survival compared those in the general population, possibly leading to survivorship bias. This requires further study.

The observed decline over time in the age-adjusted CVD incidence may suggest improved awareness, prevention (including switching from drugs associated with an increased risk of diabetes mellitus[4] and myocardial infarction[5,6]), and increased attention to managing traditional risk factors for these conditions. It may also reflect an increasing proportion of individuals living at high CD4 cell counts (because of the trend over time to start ART at higher CD4 cell counts, but also due to an increase in the proportion of individuals who have used ART long enough to reach high CD4 cell counts). A recent paper from the RESPOND cohort study confirmed our own findings that also in the current era, a significant association between CVD incidence and recent abacavir use continues to be visible and is not explained by preferential use of abacavir in individuals at increased CVD or CKD risk[7]. Apart from the association of incident CVD with abacavir-use, another recent paper from the RESPOND cohort study confirmed our finding that the use of

integrase inhibitors was associated with an increased risk of incident CVD, although statistical power was low and potential for unmeasured confounding and channelling bias cannot fully be excluded[8].
When looking at secondary CVD events, we observed a decreased risk over time in men, whereas it increased for women. This increase is thus far unexplained and needs more study.
Importantly, individuals who had initiated ART earlier after HIV acquisition (i.e. within 12 months of a last negative HIV test), had a significantly lower risk of type 2 diabetes mellitus (RR 0.60, 95% CI 0.41-0.87, p=0.007), independent of other traditional and HIV-related risk factors. The observation that the age-standardised incidence ratios for diabetes mellitus increased in women requires further study – but the observed increasing average BMI and high (and continuously increasing) prevalence of obesity in women might partially explain this observation. Finally, the general risk factors observed for diabetes mellitus and CVD (including age, hypertension, smoking, and obesity) were similar to those previously reported in other studies[9–11]. Several of these risk factors are more prevalent among people with HIV[12].

Overweight and obesity

The clinical significance of the continued increase in the prevalence of obesity over time in women, especially in migrant women from non-Western countries, requires further study. Males in all age strata were less often overweight or obese than the general Dutch male population, while women in all age strata were much more likely to be obese. Recent results suggest that weight gain after starting ART is associated with lower mortality for normal-weight individuals, but they show no clear benefit for overweight or obese individuals[13]. However, another study found that weight gain after starting ART 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[14]. 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 population of PWH, and to study the impact of interventions, such as the use of statins and antihypertensive therapy, in modifying disease risk.

In our cohort, we found that obesity and being overweight were significant risk factors for developing new-onset diabetes, cardiovascular disease and CKD, but and non-AIDS malignancies. Obese and overweight adults had a significantly lower risk of death than those with an ideal body weight, although this is likely biased by reverse causality, as body weight was included as a time-updated

variable in our regression analyses. Currently, analyses are underway in our cohort to look in depth at the relationship between weight gain on ART and the use of specific antiretroviral drugs (the integrase strand transfer inhibitors and tenofovir alafenamide, in particular) while controlling for demographic characteristics, traditional risk factors, and confounders.

Renal insufficiency

Since 2008, there has been a steady increase in the incidence of new-onset chronic kidney disease (CKD). As expected, older individuals and those with traditional risk factors such as hypertension were found to be at increased risk of CKD, as were individuals with advanced immunodeficiency. The age-standardised incidence ratio in men and women was significantly lower in the 2020-2023 period. In addition, other studies have also reported hepatitis B and C virus co-infection[15,16], and the use of tenofovir disoproxil fumarate, atazanavir/ritonavir and lopinavir/ritonavir, to be additional independent predictors of chronic renal impairment[17]. Moreover, renal impairment in the population with HIV is associated with an increased risk of cardiovascular disease[18]. The increase in CKD in our population appears to be largely caused by the more frequent 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 age-stratified incidence of non-AIDS-defining malignancy (including non-melanoma skin cancer) was significantly higher in men than the observed cancer incidence in the general Dutch male population. The relatively low cumulative follow-up time and number of events per age-group in women limits the statistical power of the analysis. However, the observed incidence in each age group appears to be rather similar to the observed cancer incidence in the general Dutch female population. The most common non-AIDS-defining malignancies (NADM) in the Netherlands are lung, intestinal, anal, prostate, and head and neck cancers, as well as Hodgkin's lymphoma. Despite the increasing average age of the cohort, the crude incidence of NADM has remained stable over time, and we even observed a decline in age-standardised incidence of NADM in men, and to a lesser extent in women. In addition, our analyses showed that individuals diagnosed with NADM a more likely to be older. This is in line with data from other cohorts, including the Swiss HIV cohort and RESPOND cohort [19–23]. Additional risk factors for NADM identified in our analyses were: current or past smoking; a CD4 cell count below 350 cells/mm^3; not being on ART, or having been pre-treated with NRTI before the start of ART; and a prior AIDS diagnosis. Other studies have reported that the effect of immunodeficiency may be stronger for infection-related non-AIDS-defining

malignancies[24]. Importantly, individuals who had initiated ART earlier after HIV acquisition (i.e. within 12 months of a last negative HIV test), had a somewhat lower risk of NADM (RR 0.77, 95% CI 0.57-1.05, p = 0.097), independent of other traditional and HIV-related risk factors.

Multimorbidity and polypharmacy

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

Polypharmacy, defined as the concomitant use of five or more medications in addition to ART, is also slowly becoming more prevalent, mainly because of the increased age of the cohort and the associated rise in the prevalence of age-associated, non-AIDS comorbidities. In 2000, 3.2% of adults used five or more non-antiretroviral comedications alongside their ART regimen, and this steadily increased to 16.0% of adults in active follow up in 2023. 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. Polypharmacy was also strongly and independently associated with an increased risk of death, independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities.

SARS-CoV-2 and COVID-19

In 2023 the number of registered SARS-CoV-2 infections (n=463) and COVID-19-related hospitalizations (n=29) dropped sharply. In 2023, just 2 people with HIV were reported to have died as a direct consequence of COVID-19 in the Netherlands.

Introduction

Since the introduction of combined antiretroviral therapy (ART) in 1996, the life expectancy of people with HIV (PWH) has markedly improved[25]; in a subgroup of recently-diagnosed, effectively-treated individuals, it was shown to be similar to that of the general population in the Netherlands[26]. Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased[27], morbidity and/or mortality associated with non-AIDS-related diseases has increased among PWH during the ART era[28–33]. Examples of these include renal and liver disease, diabetes mellitus, myocardial infarction, stroke, osteoporosis, and non-AIDS-defining malignancies.

Various reports suggest that the risk of non-AIDS-related morbidity may be higher in individuals with HIV treated with ART, than in individuals without HIV of comparable age[9-11]. For example pulmonary hypertension[37], bone disease, and non-traumatic bone fractures13-15 have each been reported to be more common in PWH. Just as with individuals without HIV, traditional risk factors (such as tobacco use[41], alcohol abuse, and viral hepatitis co-infection[42]) also contribute to the increased risk of certain non-AIDS-related comorbidities in people 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 PWH include metabolic abnormalities such as dyslipidaemia; insulin resistance; hypertension; diabetes; and changes in body composition, which may be driven partly by the use of ART, as well as by sustained, residual HIV-associated immune activation and inflammation, despite effective ART[43,44].

In this chapter, we report on mortality and its causes for adult (18 years and over) PWH using updated stichting hiv monitoring (SHM) data. We look at a total of 31,096 adult individuals ever registered by SHM – which includes 661 individuals who were diagnosed with HIV as children and have since become adults. In addition, we report on the incidence of AIDS and non-AIDS comorbidities, particularly diabetes mellitus, cardiovascular disease, chronic kidney disease (CKD), and non-AIDS malignancies in PWH.

Definitions

AIDS is defined as having experienced any of the United States' Centers for Disease Control (CDC) category C conditions[45]. In contrast to the US approach, a CD4 cell count below 200 cells/mm^3 in the absence of an AIDS-defining condition, does not qualify as AIDS in our analyses.

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

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

Chronic kidney disease (CKD) is defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min (estimated with the Cockcroft-Gault equation), confirmed after six months or longer. We use this period of time because of the large number of episodes of renal dysfunction that revert shortly after three months, and therefore do not represent true CKD.

Methods

For the analyses of incidence per calendar year and calendar period, we have considered all events after an individual entered care following HIV-1 diagnosis, or after the start of routine collection of data on the condition of interest, whichever was most recent. For instance, data on CKD were analysed from April 2007 onwards, because that was when routinely-collected renal laboratory data became available for analysis.

As the average age of the Dutch HIV population has increased over time, we also estimated the incidence rates for the periods 2000-2009, 2010-2019, and 2000-2023. We standardised these estimates according to the age distribution of the population during the period 2020-2023 (divided into the following age classes: 18-29, 30-39, 40-49, 50-59, 60-69, and 70 years and over), using the indirect method[46]. Indirect standardisation compares the incidence rates in the study and reference (period: 2020-2023) populations by applying the stratum-specific rates in the reference population to the study population. We investigated risk factors for AIDS, death, and each of the non-AIDS events, as well as a combined non-AIDS endpoint (defined as first occurrence of cardiovascular disease, diabetes mellitus, or non-AIDS-defining malignancy). CKD was not included in this combined endpoint as serum creatinine was not part of routine data collection before 2007.

The baseline for treated and untreated PWH was defined as the date of HIV-1 diagnosis or January 2000, whichever was most recent. Subsequent follow-up time was divided into periods of three months. Poisson regression models were used to estimate the independent association between risk factors and each endpoint. Models were adjusted for:

- the most recent CD4 cell count (lagged by three months);
- body mass index;
- gender;
- region of birth;
- most likely mode of HIV-1 transmission;
- current age;
- having started ART within 12 months of the last negative HIV test;
- known time spent with CD4 cell count below 200 cells/mm^3;
- known time spent with plasma HIV RNA above 1,000 copies/ml while on ART;
- time on ART;
- specific antiretroviral drugs used;
- prior diagnosis of AIDS;
- presence of chronic active hepatitis B and/or C virus infection;
- hypertension, diabetes mellitus, and other chronic comorbidities;
- smoking; and
- calendar period.

Mortality

Mortality was investigated in all 31,096 adult PWH ever registered in the SHM database. The mortality rate was 18.2 (95% confidence interval [CI] 13.5-23.9) per 1,000 person years of follow up (PYFU) in 1996 and declined to 8.9 (95% CI 7.4-10.6) per 1,000 PYFU in 2010. It has since remained stable at that 2010 level up to 2022, but the observed mortality rate was noticeably higher in 2021 during the COVID-19 pandemic with 10.8 (9.4-12.2). In 2023 the observed crude mortality rate had increased to 11.5 (10.0-13.0) per 1,000 PYFU (*Figure 5.1A*). Despite the overall improvement over time, the mortality rate in adult PWH remained well above the age-matched and gender-matched mortality observed in the general population in the Netherlands, which was 5.7 per 1,000 PYFU in 2023. The ratio of the observed mortality among PWH compared to the age/sex-adjusted mortality observed in the general population, decreased from 9.94 in 1996, to 6.54 in 2000, to 5.83 in 2005, to 3.03 in 2010, to 2.33 in 2015 and has remained constant at around 2.0 since 2017. In 2023 the ratio was 2.01.

This excess mortality can be only partly ascribed to individuals who already had AIDS at the time of their HIV diagnosis, even less so in recent years. When these individuals were excluded from the analysis, the mortality rate decreased from 14.1 (9.8-19.6) per 1,000 PYFU in 1996 to 10.4 (8.9-12.0) per 1,000 PYFU in 2023.

We repeated the analysis of mortality for various sub groups of interest (*Figure 5.1C*). The analyses were stratified based on region of origin (native Dutch, migrants with Western background, and migrants with non-Western background), HIV transmission category (men who have sex with men, other men who acquired HIV heterosexually, and women) and pre-ART nadir CD4 count (0-199, 200-499, and 500 and more cells/mm^3). The "Ratio in 2023" mentioned in the top right corner of each panel is the ratio of the observed crude mortality rate over the age/sex-adjusted expected mortality in 2023. In all investigated sub groups, the ratio of the observed over expected mortality declined over time but at the end of follow-up in 2023 remained substantially higher than one. The native Dutch, MSM, and those with higher pre-ART nadir CD4 counts had the lowest excess mortality. The observed excess mortality in the sub group who had a pre-ART nadir CD4 count of 500 and more cells/mm^3 was partly driven by a high rate of non-natural causes of death (27.4% of the 84 observed deaths in this sub group were classified to be from non-natural causes: accidents, violence, suicide, euthanasia, substance abuse, psychiatric disease).

Underlying causes of death

Observed underlying causes of death are presented in *Appendix Table 5.1.* Although the AIDS-related death rate has decreased significantly since the advent of ART, the continued occurrence of deaths due to AIDS is driven largely by the persistent high proportion of newly diagnosed people with HIV who present late for care with advanced immune deficiency. As such, the rate falls short of the aim of zero AIDS-related deaths by 2027, as stated in the Netherlands' Updated National Action Plan on STIs, HIV and Sexual Health, 2023-2027[47]. *Table 5.1* shows the characteristics of adults with HIV who died of AIDS, compared to those who died of non-AIDS causes during the last 10 years, the period 2014-2023. Individuals who died of AIDS were more frequently female, non-MSM and/or migrants, more recently diagnosed with HIV, had been on ART for a shorter period of time, and had much lower CD4 cell counts at diagnosis (58.6% had advanced HIV at diagnosis with a CD4 cell count below 200 cells/mm^3). In addition, these individuals had much lower nadir CD4 cell counts. In 49.8% of cases, they did not have controlled viremia, and 23.2% of this group was not receiving any ART at the time of death, either because ART had not been started or had been discontinued (*Table 5.1*).

Among individuals who died of AIDS but did not classify as late or advanced presenters (i.e. they had a CD4 cell count above 350 cells/mm^3 at diagnosis), the cause of death was relatively more likely to be an AIDS-related haematological malignancy, which are also known to occur in people on suppressive ART with high CD4 cell counts. The proportion and absolute number of deaths due to non-

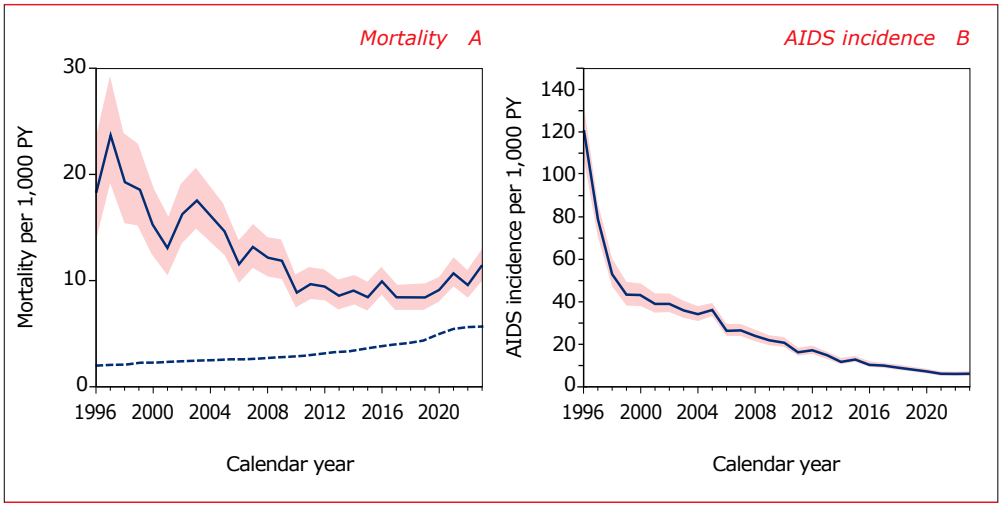
AIDS-defining conditions have increased significantly over time (*Figure 5.1.D*), primarily as a consequence of the ever increasing size and increasing average age of the population of people with HIV in the Netherlands. People with HIV who were born in the Netherlands, MSM and men in general are overrepresented among those who died of non-AIDS causes, because people in these three (overlapping) categories have a higher average age compared to migrants, HIV transmission categories other than MSM, and women. Independent risk factors for death and for being diagnosed with an AIDS-defining condition are listed in *Appendix Table 5.2*.

***Table 5.1:** Characteristics of adults with HIV who died of AIDS compared to adults with HIV who died of non-AIDS causes in the period 2014-23.*

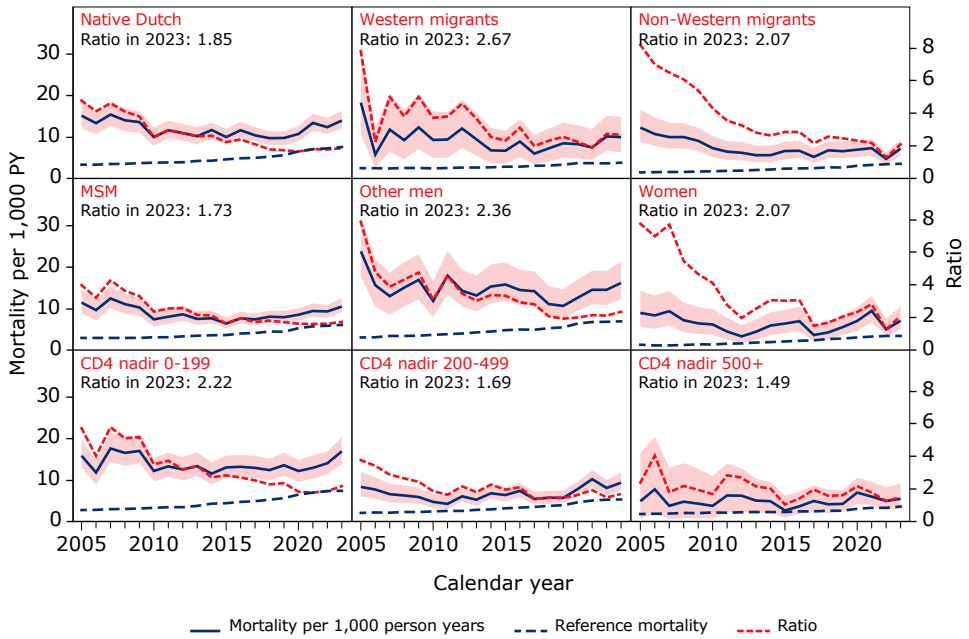
	Died of AIDS	Died of non-AIDS causes	p-value
Number of subjects	220 (11.6%)	1676 (88.4%)	
Age	56.2 (46.9-65.2)	61.1 (53.3-69.7)	<.001
Transmission category			<.001
MSM	98 (44.5%)	957 (57.1%)	
Other men	72 (32.7%)	375 (22.4%)	
Women	35 (15.9%)	179 (10.7%)	
Transgender	3 (1.4%)	11 (0.7%)	
IDU	7 (3.2%)	118 (7.0%)	
Blood contact	0 (0.0%)	33 (2.0%)	
Pediatric	5 (2.3%)	3 (0.2%)	
Region of origin			0.003
Native Dutch	139 (63.2%)	1187 (70.8%)	
Western migrants	16 (7.3%)	140 (8.4%)	
Non-Western migrants	62 (28.2%)	345 (20.6%)	
Unknown origin	3 (1.4%)	4 (0.2%)	
Years since HIV diagnosis	8.61 (0.72- 18)	16 (9.34-22.9)	<.001
Years since start cART	6.03 (0.43-13.8)	13.7 (7.28-19.2)	<.001
CD4 at HIV diagnosis	140 (50-336)	300 (120-517)	<.001
Late HIV diagnosis (CD4<350 at entry in care)	166 (76.5%)	936 (55.9%)	<.001
Advanced HIV diagnosis (CD4<200 at entry in care)	129 (58.6%)	611 (36.5%)	<.001
CD4 nadir	60 (20-134)	150 (57-262)	<.001
Last CD4 measured before death	170 (50-350)	507 (320-720)	<.001
Not undetectable at date of death	105 (49.8%)	1448 (86.8%)	<.001
Not on cART at date of death	51 (23.2%)	149 (8.9%)	<.001

***Legend:** ART = combination antiretroviral therapy. Data shown are n (%) for categorical variables and median (interquartile ranges) for continuous variables. CD4 cell counts are expressed as cells/mm^3, IDU = intravenous drug use.*

Figure 5.1.A-D: *(A) Annual mortality and (B) incidence of AIDS in 31,096 PWH in the Netherlands after entry into HIV care from 1996 onwards. (C) Annual mortality in various sub groups of interest after entry into HIV care from 2000 onwards. Solid lines represent the incidence, while the shaded areas are the 95% confidence intervals. The dashed line is the mortality rate for age-matched and sex-matched individuals from the general population in the Netherlands. The "ratio" is the ratio of observed over age/sex-standardized mortality in the Netherlands in 2023. (D) Relative changes in causes of death in different calendar periods since the introduction of combination antiretroviral therapy (ART) in the Netherlands. The numbers at the top of each bar represent the total number of deaths and the total number of individuals that were at risk during that calendar period. Mortality attributed to 'alcohol use' refers to deaths due to complications of alcohol-related liver cirrhosis.*



Mortality over time by group *C*



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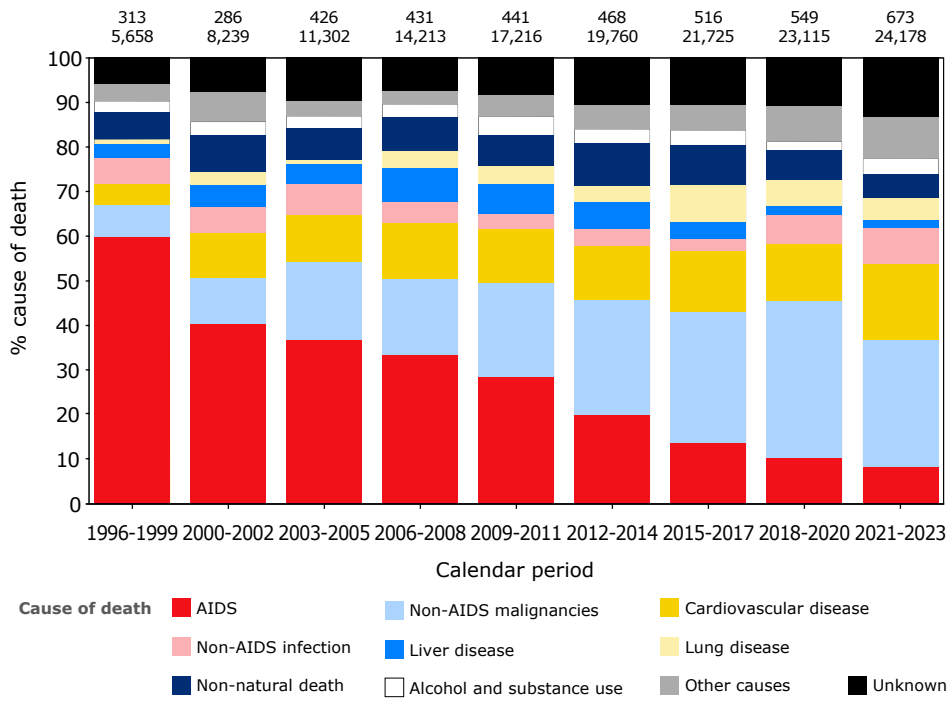


Risk factors associated with mortality

We used Poisson regression analysis to examine factors associated with mortality in individuals from the moment they started ART. After correction for all variables listed in *Appendix Table 5.2*, including time-updated age and time-updated lagged CD4 cell counts, we found that, in general, risk of death was higher in (heterosexual) men compared to women, and this risk increased as individuals grew older. It also increased if they:

- belonged to the HIV transmission risk group of people who use/used injecting drugs (PWID);
- had a prior AIDS diagnosis;
- were co-infected with the hepatitis B virus (HBV) or hepatitis C virus (HCV);
- were underweight;
- were current or past smokers;
- had spent more time with an HIV RNA level above 1,000 copies/ml while on ART; or
- had a current CD4 cell count less than 750 cells/mm^3, with the risk of death progressively increasing in lower CD4 strata.

Although a lower mortality risk was observed in individuals of non-Dutch origin, this is likely due to a larger proportion of migrants becoming lost to care (*Appendix Table 5.3*). In native Dutch individuals the risk of becoming lost to care was not linked to their CD4 cell count. In contrast, people from all other non-Dutch groups were far more likely to become lost to care if they had very low CD4 cell counts. One explanation could be that those born overseas often return to their families in their country of origin when they experience a severe deterioration in health. As a result, it is likely that mortality rates in these groups have been considerably underestimated.

Suicide and euthanasia

Individuals who had a psychiatric disease as the recorded underlying cause of death, and for whom the immediate cause of death was recorded as suicide, have been re-classified as 'suicide' for the current analysis (*Appendix Table 5.1*). The number of recorded suicides among people with HIV in the Netherlands in the period 2011 to 2023 was stable at around ten recorded cases per calendar year, which is a much higher rate than the known rates of suicide in the general Dutch population. The latter has been stable in the last 10 years; at between 10.4-11.2 instances per 100,000 individuals per year, compared to more than 40 instances per 100,000 person years in the population with HIV[48].

For patients with a serious somatic condition, who opted for euthanasia in the terminal disease stage, the underlying somatic condition was recorded as the cause of death. In the entire follow-up period from 1996 to 2023, a total of 183 instances of euthanasia were recorded; 28% of cases occurred in patients who died of AIDS, 39% in patients who died of non-AIDS-defining malignancies, and the remaining 33% in patients who died of other diseases. Our definition of euthanasia does not include the use of standard practice palliative care, like palliative sedation in the terminal phase of the underlying disease.

AIDS-defining events

In the group of 31,096 adult PWH ever registered in the SHM database, the incidence of first AIDS-defining events decreased sharply from 121.0 (95% CI 108.5-134.6) in 1996 to 6.3 (5.3-7.5) cases per 1,000 PYFU in 2023 (*Figure 5.1B*). *Appendix Table 5.4* gives an overview of the first AIDS-defining events occurring between 1996 and 2023. The most common first AIDS-defining events between 2000 and 2023 (n=575) were:

- Pneumocystis jirovecii pneumonia (23% of all events);
- esophageal candidiasis (19%);
- recurrent bacterial pneumonia (10%);
- Kaposi's sarcoma (9%);
- AIDS-defining lymphoma (8%);
- tuberculosis (7%, pulmonary 3%, extrapulmonary 4%);
- AIDS-related wasting (6%);
- cytomegalovirus-associated end organ disease (4%);
- AIDS dementia complex / HIV encephalopathy (3%); and
- toxoplasmosis of the brain (2%).

Risk factors for AIDS-defining events are shown in *Appendix Table 5.2*.

In the present analyses, we concentrate on the first occurrence of any AIDS-defining event after the start of ART. 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 ART; or
- were co-infected with HCV.

Because the main findings of the analysis of AIDS events after the start of ART were heavily influenced by events occurring shortly after the start of ART and/or while HIV-1 RNA was still detectable, we also analysed the incidence of CDC-B (moderately symptomatic HIV disease) and AIDS-defining events in individuals who had started ART at least one year before and had undetectable viraemia or transient low-level viraemia (i.e. 'blips'; below 200 copies/ml) at the moment the HIV-related event was diagnosed. In other words, we focused on those individuals with an optimal response to ART. Events were classified into CD4 strata based on the current or previously measured CD4 cell 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. Cervical dysplasia was excluded from this analysis.

Between 1 January 2000 and 31 December 2023, 27,402 individuals contributed a total of 285.2 thousand PYFU, during which 3,396 CDC-B and/or CDC-C (AIDS-defining events) were diagnosed. This resulted in an incidence rate of 11.9 events per 1,000 PYFU (1,870 CDC-B events, 6.6 events/1,000 PYFU; 1,526 CDC-C/AIDS events, 5.4 events/1,000 PYFU) (*Table 5.2*). As expected, the incidence rates were highest in the CD4 strata below 200 cells/mm^3. Although the incidence rates declined sharply in the higher CD4 strata, the incidence rates in the 200-349 and 350-499 cells/mm^3 strata remained substantial, with 10.6 and 5.3 AIDS-defining illnesses/1,000 PYFU, respectively. The incidence rates of AIDS-defining illnesses in the CD4 strata of 500-749 and over 750 cells/mm^3 were 2.7 (95% CI 2.4-3.1) and 1.8 (1.5-2.1) events/1,000 PYFU, respectively. Note that the incidence in the over 750 cells/mm^3 stratum is statistically significantly lower than in the 500-749 cells/mm^3 stratum. In these highest CD4 strata, the main AIDS-defining events that still occurred were:

- recurrent bacterial pneumonia;
- Kaposi's sarcoma;
- oesophageal candidiasis;
- non-Hodgkin's lymphoma;
- tuberculosis (pulmonary and extrapulmonary); and
- chronic genital Herpes simplex virus (HSV) ulcers

Appendix Table 5.6 shows the type and number of HIV-related diagnoses by CD4 strata. We repeated the Poisson regression for risk factors for AIDS, limited to individuals on ART with undetectable viral load and a current CD4 count of at least 500 cells/mm^3. We found that the main risk factor for incident AIDS-defining conditions in this subgroup was higher age: compared to those aged 30-39 years old, the IRR was significantly increased in those aged 50-59 (IRR 2.31, 95%CI 1.57-3.41), 60-69 years old (2.49, 95%CI 1.63-3.82), over 70 years old (3.12, 95%CI 1.83-5.34). Of note, the nadir pre-ART CD4 count was not statistically significantly associated with incident AIDS-defining conditions in this analysis (IRR 1.04 per 100 cells/mm^3 higher, 95%CI 0.98-1.10, p=0.19).

Table 5.2: *CDC-B and CDC-C/AIDS events occurring between 2000 and 2023 in individuals on ART, while having an undetectable viral load.*

CD4 category (cells/mm^3)	CDC events (n)	CDC B events (n)	CDC C events (n)	PYFU follow-up (x1000)	Incidence rate CDC events (/1000 PY) (95%CI)	Incidence rate CDC-B events (/1000 PY) (95%CI)	Incidence rate CDC-C events (/1000 PY) (95%CI)
0-50	276	115	161	0.6	435 (385-490)	181 (150-218)	254 (216-296)
50-199	650	331	319	9.3	70.3 (65.0-75.9)	35.8 (32.0-39.8)	34.5 (30.8-38.5)
200-349	687	365	322	30.4	22.6 (20.9-24.3)	12.0 (10.8-13.3)	10.6 (9.46-11.8)
350-499	635	345	290	54.4	11.7 (10.8-12.6)	6.34 (5.69-7.05)	5.33 (4.73-5.98)
500-749	708	436	272	100.2	7.07 (6.56-7.61)	4.35 (3.95-4.78)	2.71 (2.40-3.06)
750+	440	278	162	90.3	4.87 (4.43-5.35)	3.08 (2.73-3.46)	1.79 (1.53-2.09)
Total	3396	1870	1526	285.2	11.9 (11.5-12.3)	6.56 (6.26-6.86)	5.35 (5.09-5.63)

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

Tuberculosis and atypical mycobacterial infections

Between 1 January 1996 and 31 December 2023 a cumulative total of 1,180 cases of tuberculosis were diagnosed in 980 individuals, of which 691 (58.6%) were pulmonary cases and 489 (41.4%) were extrapulmonary/disseminated tuberculosis cases. During that same period, 571 cases of atypical mycobacterial infections were diagnosed in 500 individuals: 99 pulmonary and 472 extrapulmonary cases of atypical mycobacterial infections. *Figures 5.2.A & B* and *Appendix Table 5.4* describe the incidence over calendar time of tuberculosis and atypical mycobacterial infections.

Geographical region of origin

Migrants who originated from non-Western regions (73.2% of cases, 34.9% of the population) were strongly overrepresented among the tuberculosis cases, while those who were born in the Netherlands (15.1% of cases, 51.4% of the population) were strongly underrepresented. Migrants originating from Western regions (which includes countries from eastern Europe) represented 10.9% of cases and 13.1% of the population. Region of origin was not strongly associated with the incidence of atypical mycobacterial infections. *Table 5.3* describes some key characteristics of the individuals diagnosed with either tuberculosis or atypical mycobacterial infection. In case individuals had multiple diagnoses, the date of the first event was used.

Disease-related mortality rates

5.1% of the individuals diagnosed with pulmonary tuberculosis and 4.5% of the individuals diagnosed with extrapulmonary tuberculosis died within 365 days of the diagnosis, with the reported cause of death being 'AIDS' or 'infection'. The disease-related mortality rates within 365 days of diagnosis were 6.1% for pulmonary and 17.6% for extrapulmonary atypical mycobacterial infections.

Latent tuberculosis infection screening

The current national guidelines recommend performing screening for latent tuberculosis infection (LTBI) in all individuals newly diagnosed with HIV who are at increased risk for tuberculosis (migrants from high-endemic regions or individuals who have been in close contact with cases of tuberculosis). The recommended method for LTBI screening is the interferon gamma release assay (IGRA) in combination with a tuberculin skin test (Mantoux test). Treatment of individuals in whom LTBI has been diagnosed considerably lowers their risk of developing tuberculosis.

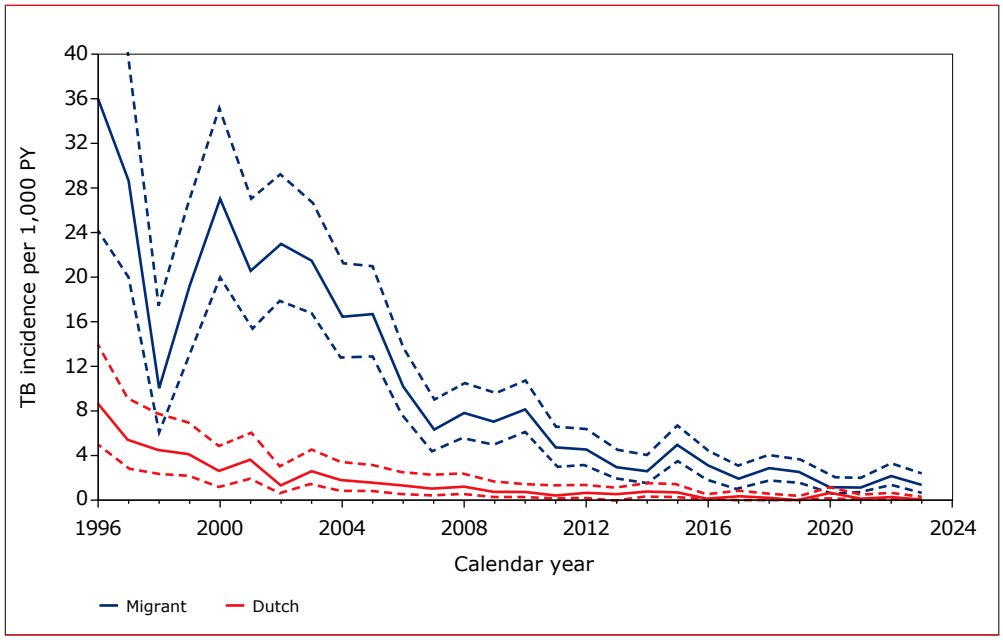
SHM has been collecting data on LTBI screening and treatment since 2018. IGRA testing during an episode in which active TB was diagnosed, was excluded from this dataset. A limitation of our analysis of LTBI screening is that we do not have data on whether, at the time of IGRA testing, the individual had complaints that may have been caused by tuberculosis, which then prompted the treating physician to perform IGRA testing. In 22.8% of cases a chest X-ray or CT-scan was taken, indicating that in some of these instances the individual might also have had pulmonary symptoms at the moment of IGRA testing.

Since 1 January 2018, SHM has recorded LTBI screening using IGRA with or without an additional tuberculin skin test in 2,394 individuals. In 232 (9.7%) of these individuals LTBI testing was positive, and 82 (35.3%) of those received a course of LTBI treatment. LTBI treatment consisted of:

- isoniazid plus rifampicin (typically for a duration of three months) in 29 individuals;
- isoniazid monotherapy (typically for a duration of six to nine months) in 42 individuals; and
- rifampicin monotherapy (typically for a duration of four months) in three individuals.

A further eight individuals received another non-standard treatment. In the 232 individuals who tested positive on LTBI screening, two cases of tuberculosis were diagnosed later during follow-up: one case of active extrapulmonary tuberculosis developed (four months after diagnosis) while that individual was receiving treatment consisting of rifampicin plus isoniazid, and one case of pulmonary tuberculosis was diagnosed 3 years after diagnosis of untreated LTBI. Of the 150 individuals with positive LTBI screening who did not receive LTBI treatment, 21 (14.0%) were known to have been diagnosed with and treated for active tuberculosis prior to the LTBI screening.

Figure 5.2.A & B: Crude incidence rates of tuberculosis and nontuberculous mycobacterial infections in Dutch and migrants per 1,000 person years of follow up (solid lines) and 95% confidence intervals (dashed lines).



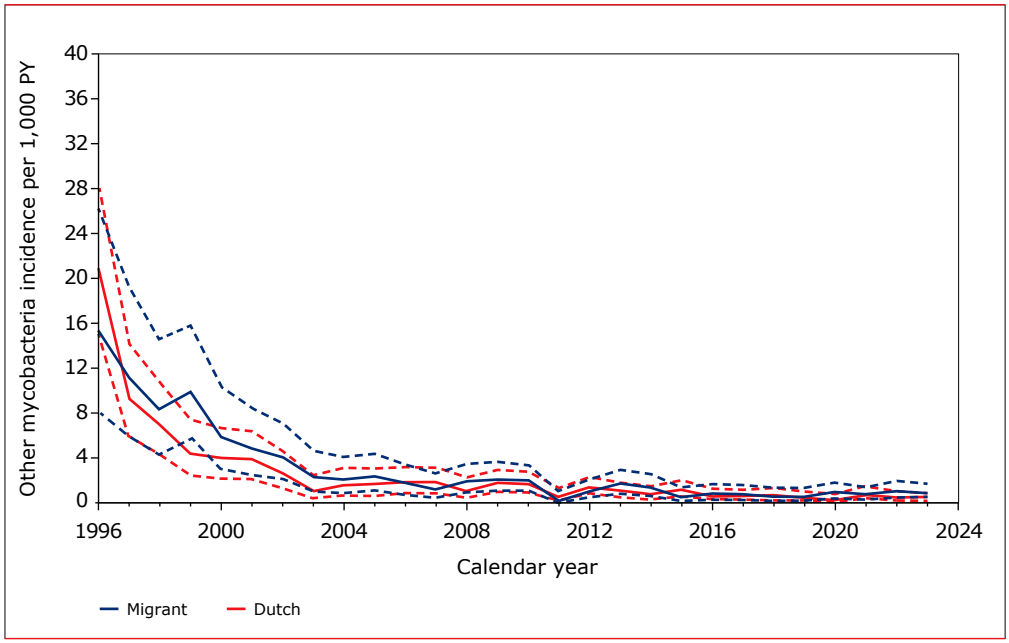


Table 5.3: Characteristics at the time individuals were diagnosed with tuberculosis or atypical mycobacterial infections for the first time.

	Tuberculosis	Atypical mycobacterial infections	p-value
Number of subjects	980 (66.2%)	500 (33.8%)	
Age	36.9 (30.6-44.5)	40 (34.5- 48)	<.001
Transmission category			<.001
MSM	206 (21.0%)	220 (44.0%)	
Other men	365 (37.2%)	149 (29.8%)	
Women	304 (31.0%)	92 (18.4%)	
Transgender	16 (1.6%)	5 (1.0%)	
IDU	60 (6.1%)	25 (5.0%)	
Blood contact	27 (2.8%)	6 (1.2%)	
Pediatric	2 (0.2%)	3 (0.6%)	
Region of origin			<.001
Native Dutch	176 (18.0%)	279 (55.8%)	
Western migrants	90 (9.2%)	50 (10.0%)	
Non-Western migrants	709 (72.3%)	171 (34.2%)	
Unknown origin	5 (0.5%)	0 (0.0%)	
Diagnosed before HIV diagnosis	225 (23.0%)	32 (6.4%)	<.001
Years since HIV diagnosis	0.92 (0.5- 4.7)	1.12 (0.57- 6.5)	0.007
Years since start cART	0.42 (0-1.16)	0.62 (0.25-1.22)	<.001
CD4 at HIV diagnosis	199 (61-400)	40 (10-200)	<.001
Late HIV diagnosis (CD4<350 at entry in care)	444 (68.5%)	368 (84.6%)	<.001
Advanced HIV diagnosis (CD4<200 at entry in care)	656 (66.9%)	391 (78.2%)	<.001
CD4 nadir	120 (40-250)	20 (10- 50)	<.001
Last CD4 measured before event	210 (102-370)	90 (30-190)	<.001
Not undetectable at date of event	172 (17.6%)	121 (24.2%)	0.003
Not on cART at date of event	702 (71.6%)	247 (49.4%)	<.001

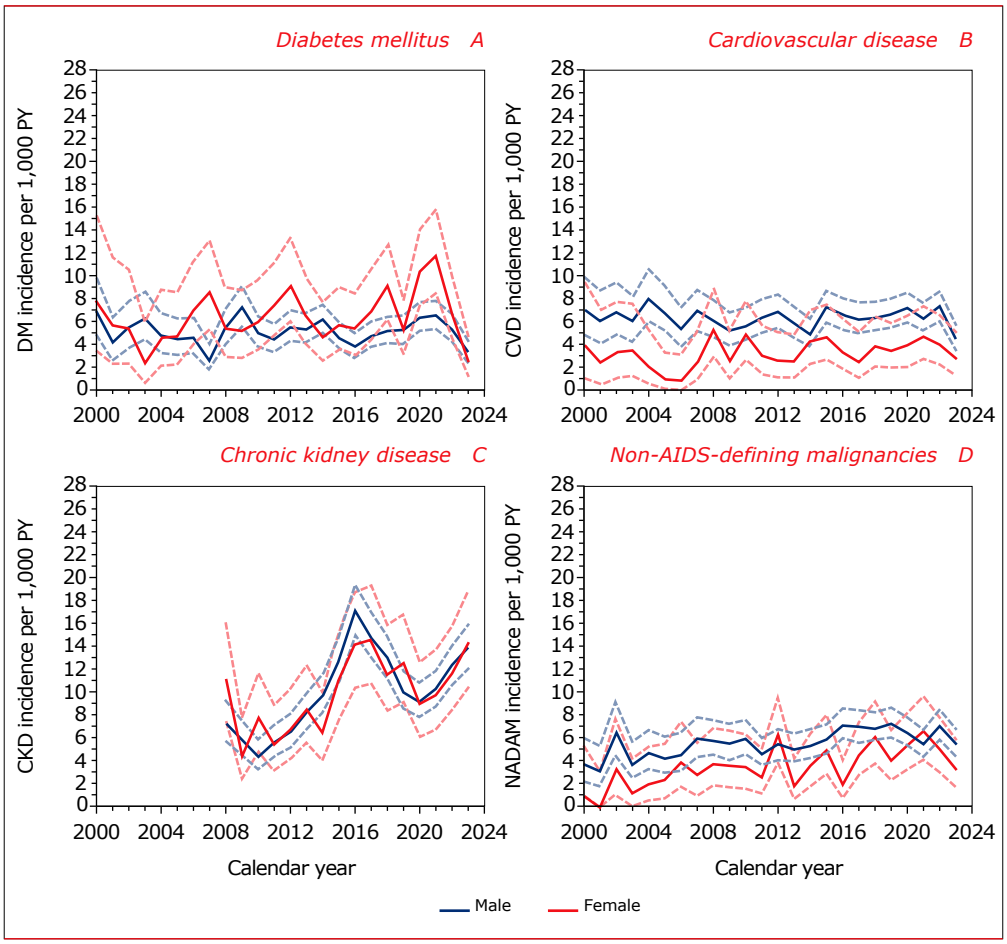
Non-AIDS-defining events

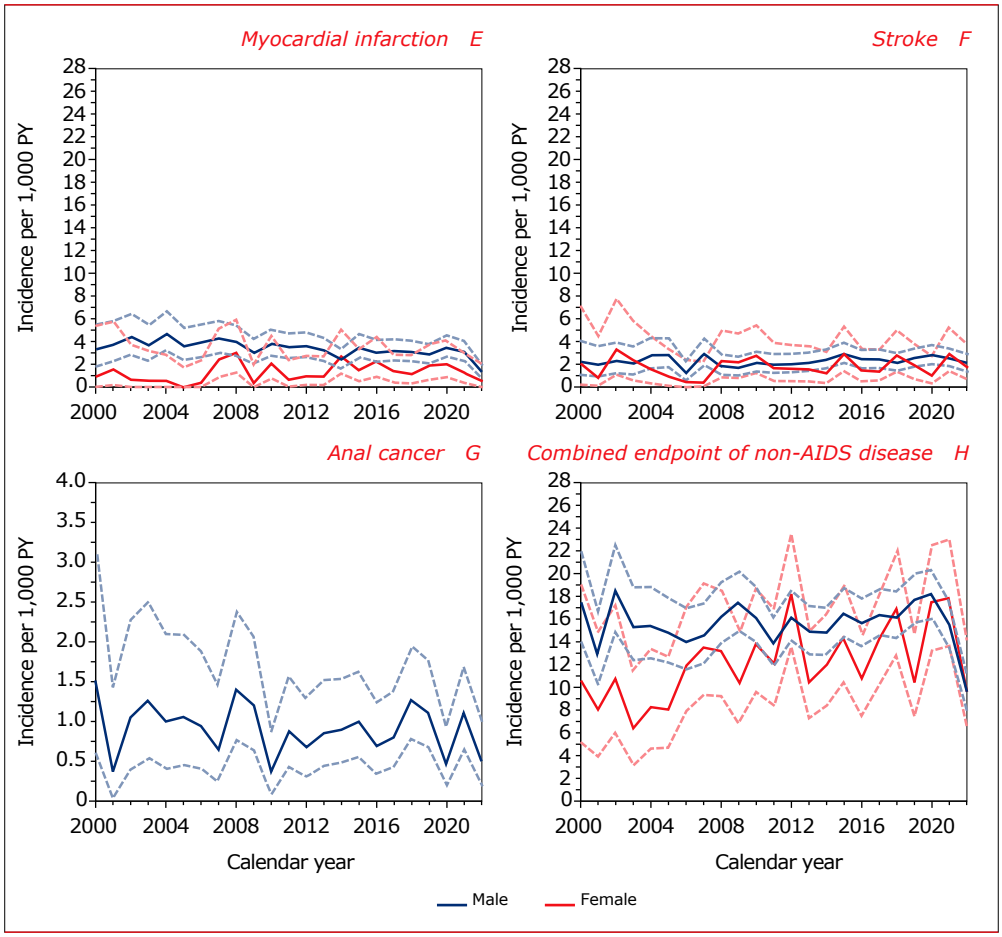
Of the 31,096 adult PWH ever registered with SHM, 30,747 were aged 18 years and over while in follow up in, or after January 2000. For these treated and untreated adults, we report incidence figures and risk factors for:

- diabetes mellitus;
- a composite cardiovascular disease endpoint (and also separately for myocardial infarction and stroke);
- non-AIDS-defining malignancies (both overall and separately for anal cancer); and
- chronic kidney disease (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 5.3.A-H*).

Figure 5.3.A-H: *Crude incidence rates per 1,000 person years of follow up (solid lines) and 95% confidence intervals (dotted lines) of (A) diabetes mellitus, (B) cardiovascular disease, (C) chronic kidney disease, (D) non-AIDS-defining malignancies, (E) myocardial infarction, (F) stroke, (G) anal cancer, and (H) combined endpoint of non-AIDS disease (diabetes mellitus, cardiovascular disease, and non-AIDS-defining malignancies), by gender, with the exception of anal cancer, which is presented for males only.*





Diabetes mellitus

Of the 30,747 individuals aged 18 years and over, who were in follow up in, or after January 2000, a total of 1,898 (1,457 men and 441 women) were diagnosed with type 2 diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 5.3A*), and in 2023 was 3.2 (95% CI 2.4-4.3) per 1,000 PYFU in men and 2.4 (1.0-4.7) per 1,000 PYFU in women. In men, the age-standardised incidence ratio declined over time and was significantly lower in 2010-2019 and 2020-2023 than in 2000-2009. In women, however, an opposite effect was seen, as the age standardised incidence in significantly increased over the observation period (*Table 5.4A*).

Demographic and clinical factors independently associated with an increased risk of new-onset diabetes mellitus were:

- non-Dutch/Western origin;
- older age group;
- a BMI greater than 25 kg/m^2 or below 18 kg/m^2;
- hypertension;
- a latest CD4 cell count below 200 cells/mm^3;
- pre-treatment with nucleoside analogue reverse transcriptase inhibitors (NRTIs) prior to starting ART (in particular zidovudine and didanosine);
- treatment with the integrase inhibitors bictegravir, dolutegravir or raltegravir (but not elvitegravir and cabotegravir) and
- a prior AIDS diagnosis (*Appendix Table 5.5*).

Moreover, the risk of new-onset diabetes in the periods 2000-2009 and 2010-2019 was significantly higher than in the period 2020-2023. Starting ART within 12 months of the last negative HIV test was also associated with a lower risk of new-onset diabetes. Note that multivariate analysis showed that the higher age-adjusted incidence rates of diabetes in women are largely explained by their higher BMI.

We compared the age- and sex-stratified prevalence of diabetes mellitus in the population of people with HIV with that observed in the general Dutch population (*Table & Figure 5.4B*). In men the prevalence of diabetes was significantly lower in nearly all age strata, while in women aged up to 65 year old the observed prevalence of diabetes was higher compared to the reference values in the general population.

Table 5.4A: *Crude incidence of diabetes mellitus per 1,000 person years of follow up in 2000–2009, 2010–2019 and 2020–2023 and age-standardised incidence ratio (indirect method) with 95% confidence intervals.*

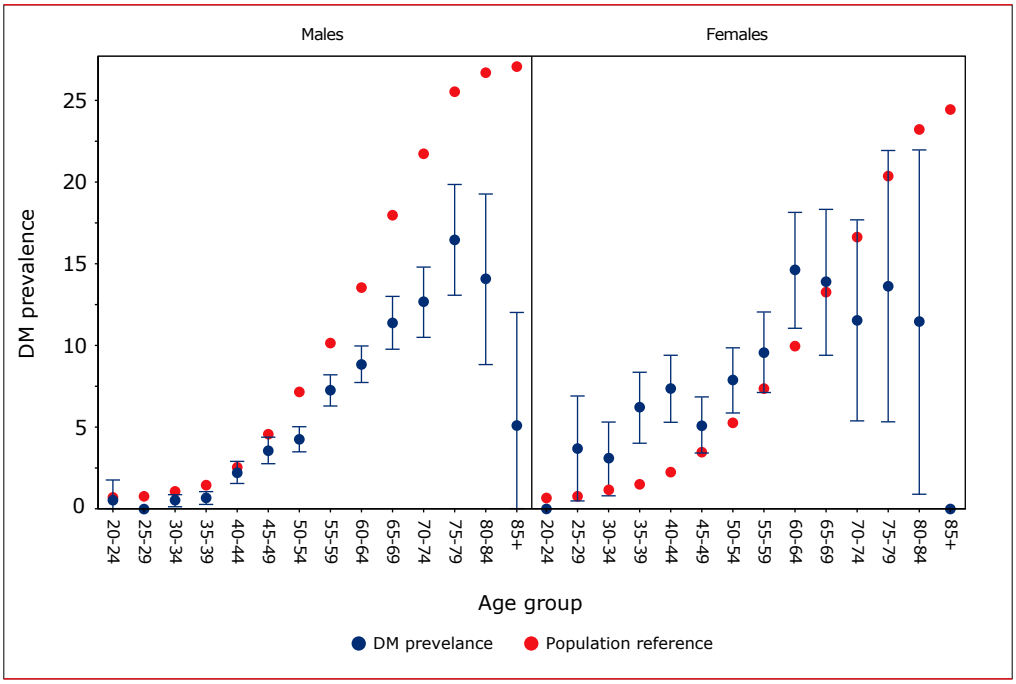
Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000–2009	5.2 (4.7–5.7)	1.28 (1.15–1.40)	5.7 (4.7–6.9)	0.75 (0.61–0.89)
2010–2019	5.0 (4.7–5.4)	1.03 (0.96–1.11)	6.6 (5.7–7.5)	0.86 (0.75–0.98)
2020–2023	5.5 (4.9–6.1)	1 (reference)	7.8 (6.5–9.4)	1 (reference)

**Standardised according to the observed age distribution between 2020–2023.*

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

Table & Figure 5.4B: *Prevalence of diabetes mellitus in people with HIV stratified by age and sex in 2023, compared to the prevalence of diabetes mellitus type 2 in the general Dutch population in 2021 (https://www.vzinfo.nl/diabetes-mellitus/leeftijd-en-geslacht, accessed 10-9-2024).*

Age group (years)	Males				Females			
	Events (n)	Group size (n)	Prevalence % (95%CI)	General population prevalence (%)	Events (n)	Group size (n)	Prevalence % (95%CI)	General population prevalence (%)
20-24	1	167	0.6 (0.0-1.8)	0.71	0	64	0.0 (0.0-0.0)	0.7
25-29	0	563	0.0 (0.0-0.0)	0.78	5	135	3.7 (0.5-6.9)	0.75
30-34	7	1,345	0.5 (0.1-0.9)	1.07	7	227	3.1 (0.8-5.3)	1.13
35-39	11	1,601	0.7 (0.3-1.1)	1.51	29	467	6.2 (4.0-8.4)	1.45
40-44	42	1,867	2.2 (1.6-2.9)	2.62	46	625	7.4 (5.3-9.4)	2.22
45-49	73	2,031	3.6 (2.8-4.4)	4.64	33	644	5.1 (3.4-6.8)	3.46
50-54	110	2,571	4.3 (3.5-5.1)	7.16	55	700	7.9 (5.9-9.9)	5.29
55-59	213	2,932	7.3 (6.3-8.2)	10.12	53	553	9.6 (7.1-12.0)	7.3
60-64	217	2,449	8.9 (7.7-10.0)	13.54	56	384	14.6 (11.1-18.1)	9.95
65-69	170	1,494	11.4 (9.8-13.0)	17.96	32	231	13.9 (9.4-18.3)	13.24
70-74	117	925	12.6 (10.5-14.8)	21.71	12	104	11.5 (5.4-17.7)	16.62
75-79	76	462	16.5 (13.1-19.8)	25.52	9	66	13.6 (5.4-21.9)	20.35
80-84	24	171	14.0 (8.8-19.2)	26.65	4	35	11.4 (0.9-22.0)	23.22
85+	2	39	5.1 (0.0-12.1)	27.02	0	11	0.0 (0.0-0.0)	24.4



Cardiovascular disease

From January 2000 onwards, 2,008 individuals (1,779 men and 229 women) experienced one or more fatal or non-fatal cardiovascular event. Of these individuals:

- 972 had a myocardial infarction;
- 751 had a stroke;
- 145 had a coronary artery bypass graft;
- 738 had a coronary angioplasty or stenting; and
- 20 had a carotid endarterectomy.

The crude incidence over time remained stable and was lower in women than in men (*Figure 5.3B*). The age-standardised incidence ratio in men and women declined over time (*Table 5.5A*).

In the analysis of risk factors, those associated with cardiovascular disease were:

- older age group;
- male gender, MSM had lower risk than other men;
- a latest CD4 cell count below 350 cells/mm^3
- a prior AIDS diagnosis; as well as having a longer duration of severe immunodeficiency defined as cumulative number of years with a CD4 count <200 cells/mm^3;
- pre-treatment with NRTIs before starting ART;
- use of abacavir (either currently or in the last six months);
- current use of dolutegravir, raltegravir or bictegravir (borderline significant) (but not elvitegravir or cabotegravir);
- current and past smoking;
- the presence of diabetes mellitus; and
- the presence of hypertension.

Estimated cardiovascular risk using the D:A:D algorithm was also higher during 2000-2009 and 2010-2019 than during 2020-2023, independent of other variables included in the analysis (*Appendix Table 5.5*). The strong positive association between use of abacavir and CVD was independent of renal function. When eGFR, estimated using the Cockcroft-Gault method (available from 2007 onwards), was included in the model the abacavir effect was only slightly attenuated, decreasing from an incidence risk ratio (IRR) of 1.47 to 1.38, $p<0.001$. Compared to having an eGFR above 90 ml/min, having an eGFR below 60 ml/min was independently associated with a higher risk of CVD:

- at 60-90 ml/min, the IRR was 1.01 (95% CI 0.89-1.30);
- at 30-60 ml/min the IRR was 1.51 (1.27-1.80);
- at 15-30 ml/min, the IRR was 4.04 (2.91-5.61); and
- at 0-15 ml/min the IRR was 3.41 (2.06-5.65).

From January 2000 onwards, 282 men and 34 women experienced a fatal or non-fatal secondary cardiovascular event: 169 had a myocardial infarction, 158 had a stroke (note that 11 persons experienced both a secondary MI and a secondary stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2023 in men and women with a prior cardiovascular event was 26.1 (23.1-29.3) and 22.3 (15.5-31.2), respectively. The crude rate and age-standardised incidence ratio (SIR; indirect method) of secondary myocardial infarction and stroke per 1,000 PYFU decreased significantly over time in men while it increased in women (*Table 5.5B*).

We compared the age- and sex-stratified prevalence of coronary artery disease (which includes myocardial infarction, angina pectoris) in the population of people with HIV with that observed in the general Dutch population (*Table & Figure 5.5C*). In men and women the prevalence of coronary artery disease was fairly equal in all age strata compared to the reference values in the general population.

***Table 5.5A-B:** Crude incidence of primary (A) and secondary (B) cardiovascular disease per 1,000 person years of follow up in 2000-2009, 2010-2019, and 2020-2023 and age-standardised incidence ratio with 95% confidence intervals.*

Primary CVD		**Male**		**Female**
Calendar year	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000-2009	6.4 (5.8-7.0)	1.75 (1.59-1.91)	2.7 (2.0-3.5)	1.45 (1.06-1.84)
2010-2019	6.3 (5.9-6.7)	1.23 (1.15-1.31)	3.5 (2.9-4.2)	1.17 (0.96-1.39)
2020-2023	6.4 (5.8-7.0)	1 (reference)	3.9 (3.0-5.0)	1 (reference)

Secondary CVD		**Male**		**Female**
Calendar year	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000-2009	31.2 (24.2-39.5)	1.54 (1.18-1.91)	15.2 (4.1-39.0)	0.46 (0.01-0.92)
2010-2019	26.4 (22.2-31.0)	1.22 (1.02-1.41)	21.0 (12.3-33.7)	0.67 (0.35-0.98)
2020-2023	22.2 (17.3-28.0)	1 (reference)	28.7 (15.3-49.1)	1 (reference)

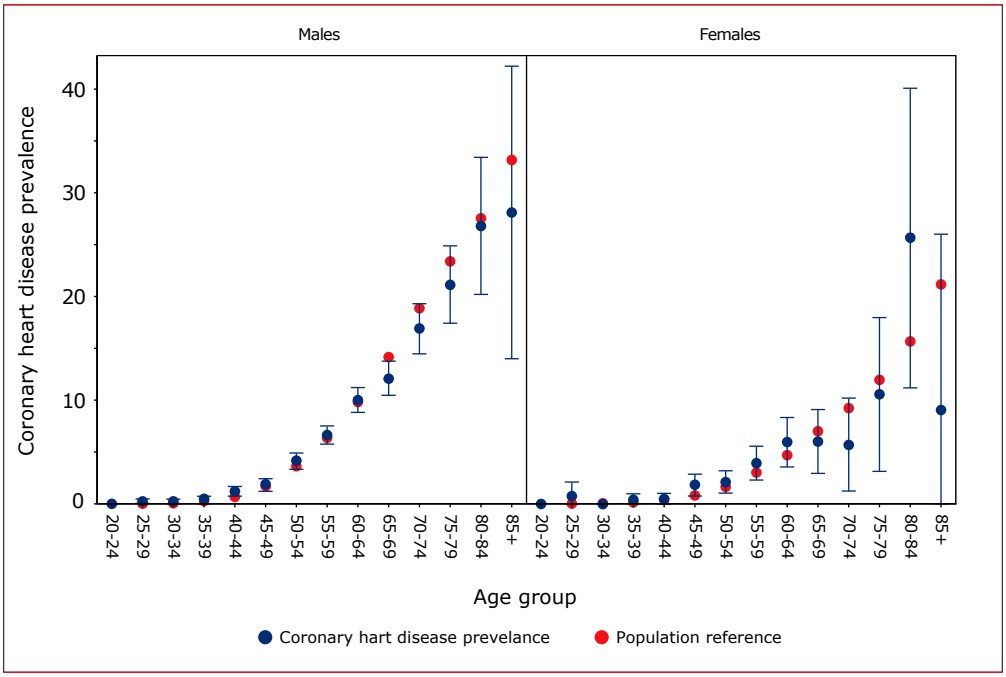
**Standardised according to the observed age distribution in 2020-2023.*

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

Table & Figure 5.5C: *Prevalence of coronary artery disease in people with HIV stratified by age and sex in 2023, compared to the prevalence observed in the general Dutch population in 2023 (https://www.staatvenz.nl/kerncijfers/coronaire-hartziekten-aantal-patiënten-bekend-bij-de-huisarts, accessed 10-9-2024).*

Age group (years)	Males				Females			
	Events (n)	Group size (n)	Prevalence % (95%CI)	General population prevalence (%)	Events (n)	Group size (n)	Prevalence % (95%CI)	General population prevalence (%)
20-24	0	167	0.0 (0.0-0.0)	0.03	0	64	0.0 (0.0-0.0)	0.02
25-29	1	563	0.2 (0.0-0.5)	0.05	1	135	0.7 (0.0-2.2)	0.03
30-34	3	1,345	0.2 (0.0-0.5)	0.1	0	227	0.0 (0.0-0.0)	0.06
35-39	7	1,601	0.4 (0.1-0.8)	0.28	2	467	0.4 (0.0-1.0)	0.12
40-44	23	1,867	1.2 (0.7-1.7)	0.64	3	625	0.5 (0.0-1.0)	0.35
45-49	38	2,031	1.9 (1.3-2.5)	1.77	12	644	1.9 (0.8-2.9)	0.82
50-54	108	2,571	4.2 (3.4-5.0)	3.59	15	700	2.1 (1.1-3.2)	1.62
55-59	196	2,932	6.7 (5.8-7.6)	6.42	22	553	4.0 (2.3-5.6)	3.05
60-64	246	2,449	10.0 (8.9-11.2)	9.85	23	384	6.0 (3.6-8.4)	4.77
65-69	182	1,494	12.2 (10.5-13.8)	14.19	14	231	6.1 (3.0-9.1)	7.03
70-74	157	925	17.0 (14.6-19.4)	18.93	6	104	5.8 (1.3-10.3)	9.26
75-79	98	462	21.2 (17.5-24.9)	23.44	7	66	10.6 (3.2-18.0)	12
80-84	46	171	26.9 (20.3-33.5)	27.61	9	35	25.7 (11.2-40.2)	15.71
85+	11	39	28.2 (14.1-42.3)	33.27	1	11	9.1 (0.0-26.1)	21.25

Legend: *CI = confidence intervals.*



Trends in cardiovascular risk factors

Figures 5.4A and *5.4B* show that the distribution of body mass index (BMI) of both men and women in the HIV-1-positive population has increased over time. In 2023, the proportion of men with available BMI data who were overweight (25-30 kg/m^2) or obese (WHO class I: 30-35 kg/m^2 and WHO class II/III: 35 kg/m^2 or over), was 36.5%, 10.0% and 2.6%, respectively. In women, these proportions were 30.9%, 20.0% and 12.2%, respectively.

Table 5.5D and *Figure 5.4C* shows a comparison with the general Dutch population of the age- and sex-stratified prevalence of overweight and obesity in 2023. Males aged 35 and older were significantly less often overweight or obese than the general Dutch male population, while women in all age strata were more likely to be obese.

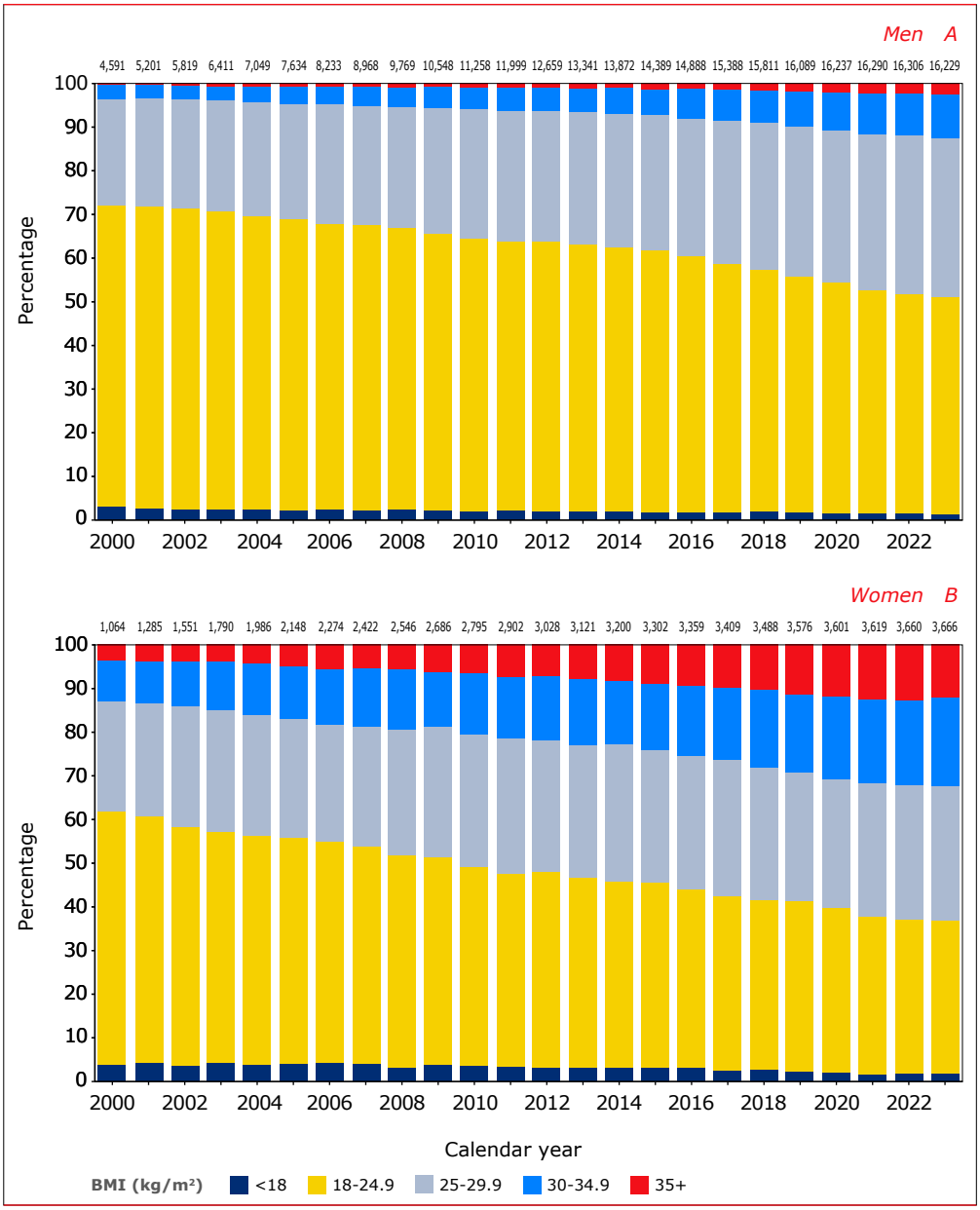
Table 5.5D: *Age- and sex-stratified prevalence of overweight and obesity in 2023, compared to the general Dutch population (source: https://www.vzinfo.nl/overgewicht/volwassenen, accessed 10-9-2024).*

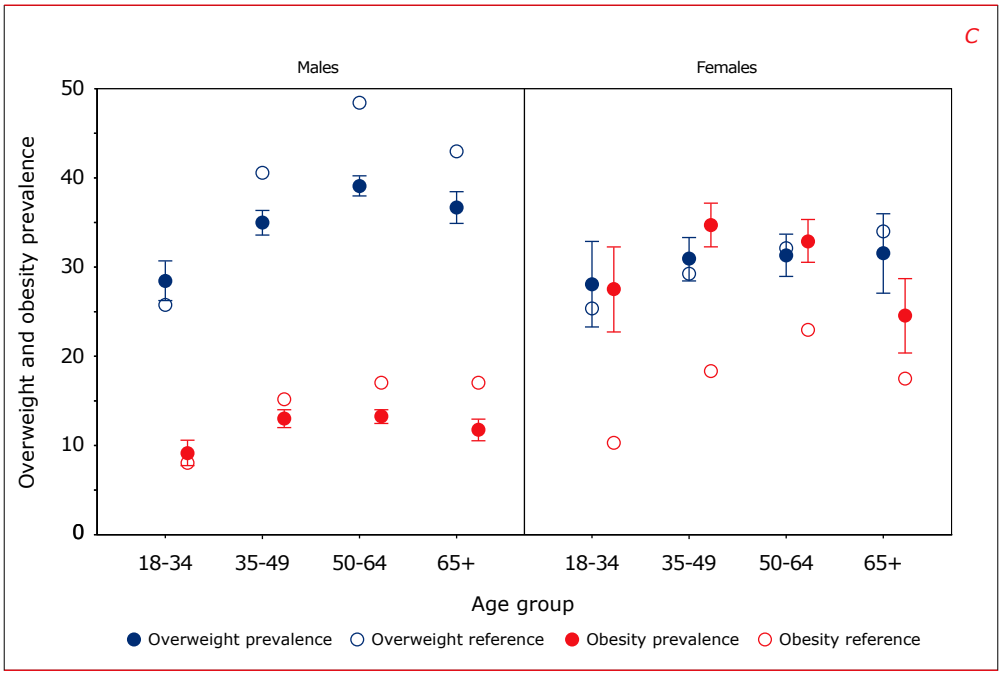
Age group (years)	Group size (n)	Over-weight (n)	Overweight prevalence % (95%CI)	General population overweight prevalence (%)	Obesity (n)	Obesity prevalence % (95%CI)	General population obesity prevalence (%)
Males							
18-34	1,582	451	28.5 (26.3-30.7)	25.8	145	9.2 (7.7-10.6)	8.1
35-49	4,634	1,623	35.0 (33.7-36.4)	40.6	605	13.1 (12.1-14.0)	15.2
50-64	7,165	2,804	39.1 (38.0-40.3)	48.4	956	13.3 (12.6-14.1)	17.1
65+	2,848	1,046	36.7 (35.0-38.5)	43	336	11.8 (10.6-13.0)	17.1
Females							
18-34	341	96	28.2 (23.4-32.9)	25.4	94	27.6 (22.8-32.3)	10.3
35-49	1,450	449	31.0 (28.6-33.3)	29.1	504	34.8 (32.3-37.2)	18.4
50-64	1,460	458	31.4 (29.0-33.7)	32.2	481	32.9 (30.5-35.4)	23
65+	415	131	31.6 (27.1-36.0)	34	102	24.6 (20.4-28.7)	17.5

Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the population with HIV. This analysis revealed that the increase was at least partially driven by changes over time in population demographic characteristics (age, non-Western region of origin, HIV transmission category) and time since first initiating ART, and that this effect was more marked in men than in women. With regard to specific antiretroviral drugs, the use of bictegravir, dolutegravir, rilpivirine and tenofovir alafenamide were all independently associated with higher body weight.

Figure 5.4C shows the distribution of BMI according to age groups in 2023 for men and women, compared to the reference proportions from the general Dutch population. Whereas in adult men of all age groups, the proportion classified as obese (12.6%) was somewhat lower than the proportion found in the general Dutch male population (13.5%), in women of all age groups there was more obesity (32.2%) than in the general Dutch female population (17.2%)[49]. There were substantial differences between those of Dutch origin, Western migrants and non-Western migrants: among males, 11.3% of Dutch men, 13.8% of Western migrants and 15.2% of non-Western migrants were obese. In females, however, those figures were 23.5%, 21.8%, and 38.5%, respectively. Being overweight (a BMI between 25-30) or being obese (a BMI over 30) were both independently associated with an increased risk of diabetes (overweight IRR 2.23, 95%CI 1.97-2.53, p<0.001; obese IRR 5.41, 95%CI 4.71-6.21, p<0.001), as well as with CKD (overweight IRR 1.15, 95%CI 1.05-.25, p=0.002; obese IRR 1.14, 95%CI 1.00-1.30, p=0.043). Being obese was independently associated with CVD (overweight IRR 1.03, 95%CI 0.92-1.15, p=0.61; obese IRR 1.22, 95%CI 1.04-1.43, p=0.015) (*Appendix Table 5.5*). Overweight and obesity were not associated with an increased risk of non-AIDS malignancies.

Figure 5.4: *Distribution of the body mass index (BMI) at the end of each calendar year in (A) men, and (B) women, as a percentage of the total number of men and women with a known BMI in each year, and (C) distribution of the BMI categories over the age groups for men, and women, in 2023, compared to the general Dutch population. 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).*





Legend: *BMI = body mass index.*

Several topics that in previous editions of the SHM Monitoring Report were part of this Chapter are in this edition of the Monitoring Report included in Chapter 9 on Quality of Care: prevalence and treatment of hypertension; the proportion of treated hypertensive individuals attaining treatment goals; the proportion of individuals with a SCORE2 or SCORE2-OP predicted 10-year risk greater than 10%, without a history of CVD, that received a prescription for statins; the proportion of high-risk individuals receiving statins who attained treatment goals.

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 the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations[50]. 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 ART. Of these equations, both the Cockcroft-Gault and the CKD-EPI equations have been validated in individuals with HIV[50,51]. However, because the CKD-EPI equation is the one most often used in clinical practice, we have chosen to report eGFR values as estimated by this equation. The distribution of eGFR categories in ml/min/1.73m^2 (90 or above, normal kidney function; 60-89, mildly reduced; 30-59, moderately reduced; 15-29, severely reduced; and below 15, very severely reduced kidney function) is shown in *Figures 5.5A* and *5.5B* for men and women. The percentage of men with normal kidney function decreased over time from 74.5% in 2007, to 41.5% in 2023, and this pattern was similar in women. Typically, eGFR decreases with increased age, as shown in *Figure 5.6*, and therefore the decrease in the proportion of individuals with normal function over time is likely due, in part, to the increasing age of individuals in care.

CKD incidence and risk factors

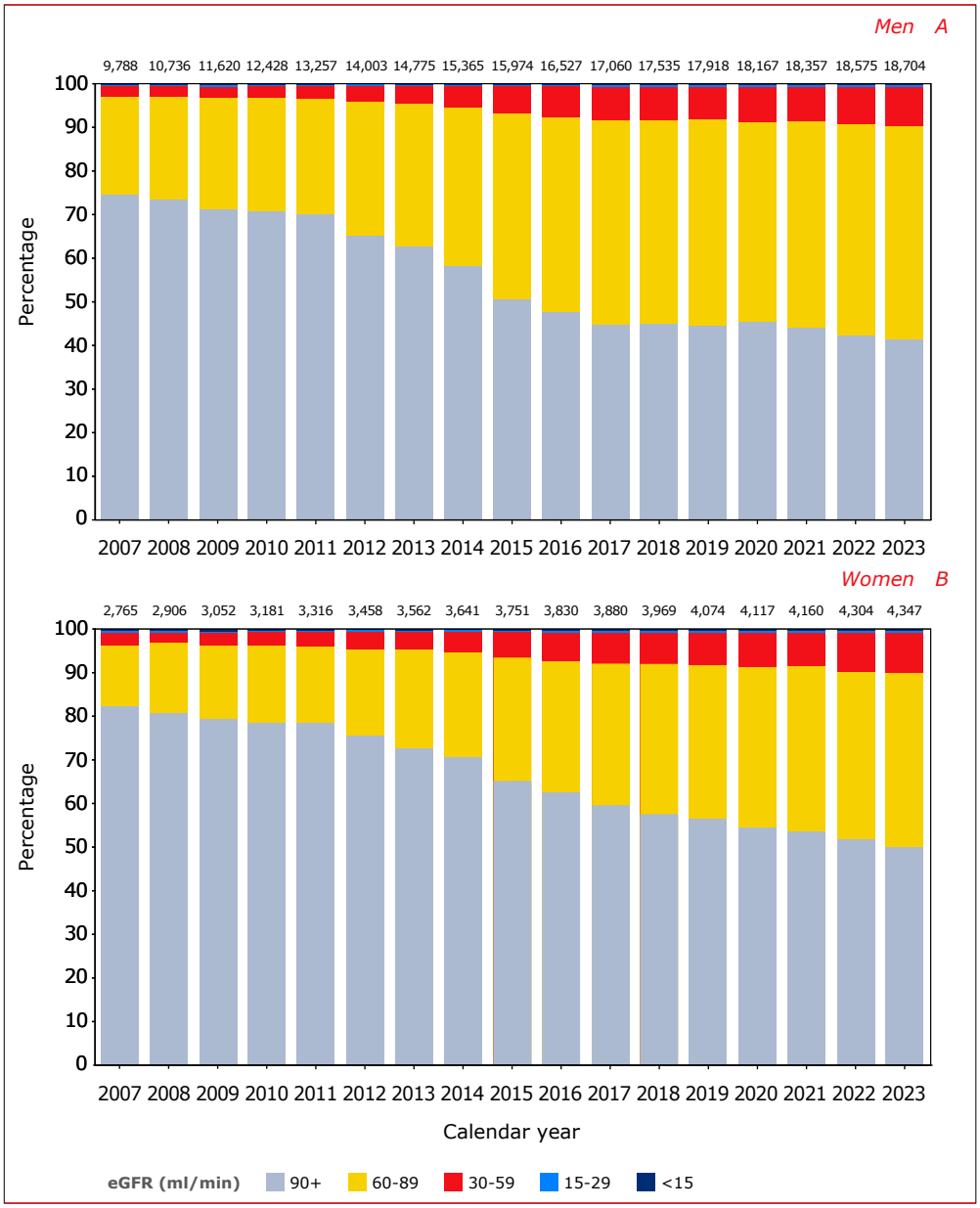
In individuals with an eGFR above 60ml/min/1.73m^2 at the time of inclusion in the analyses, who did not have a previously confirmed CKD, the crude incidence of CKD (defined as eGFR below 60ml/min/1.73m^2 confirmed by a second test at least 26 weeks later) varied over time (*Figure 5.3C*). Routine collection of serum creatinine measurements commenced in 2007. To avoid misclassifying prevalent CKD as incident CKD, we used serum creatinine levels measured in 2007 to distinguish between prevalent (i.e. CKD already present in 2007) versus new-onset incident cases of CKD (i.e. no CKD observed in 2007) from 2008 onwards. In men, the incidence rose from 9.9 cases per 1,000 PYFU in the period 2008-19 to 10.5 in 2020-23. In women, the incidence rose from 10.3 to 11.0 cases per 1,000 PYFU during the same periods (*Table 5.6*). However, the age-standardised incidence ratio in men and women was significantly lower in the 2020-2023 period (*Table 5.6*).

Risk factors for CKD included:

- female gender;
- Dutch origin;
- low current CD4 cell count (below 350 cells/mm^3);
- a prior AIDS diagnosis;
- belonging to the HIV transmission risk group of people who inject drugs;
- older age group;
- being underweight or overweight / obese;
- hypertension;
- diabetes mellitus;
- cardiovascular disease;
- pre-treatment with monotherapy and dual therapy with nucleoside analogues before the start of ART; and
- chronic HBV and HCV co-infection (*Appendix Table 5.5*).

When current use of cobicistat, rilpivirine, dolutegravir, and bictegravir were added to the model, the increased risk of CKD over calendar time completely disappeared (even reversed). This strongly suggests that the increase in CKD seen in recent years is largely due to increases in serum creatinine caused by ARV-induced reversible inhibition of two transporters that mediate tubular secretion of creatinine, without affecting the true glomerular filtration rate (namely, organic cation transporter 2 [OCT2], and multidrug and toxin extrusion transporter [MATE1]) and is therefore not a true increase in CKD.

Figure 5.5: *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.*



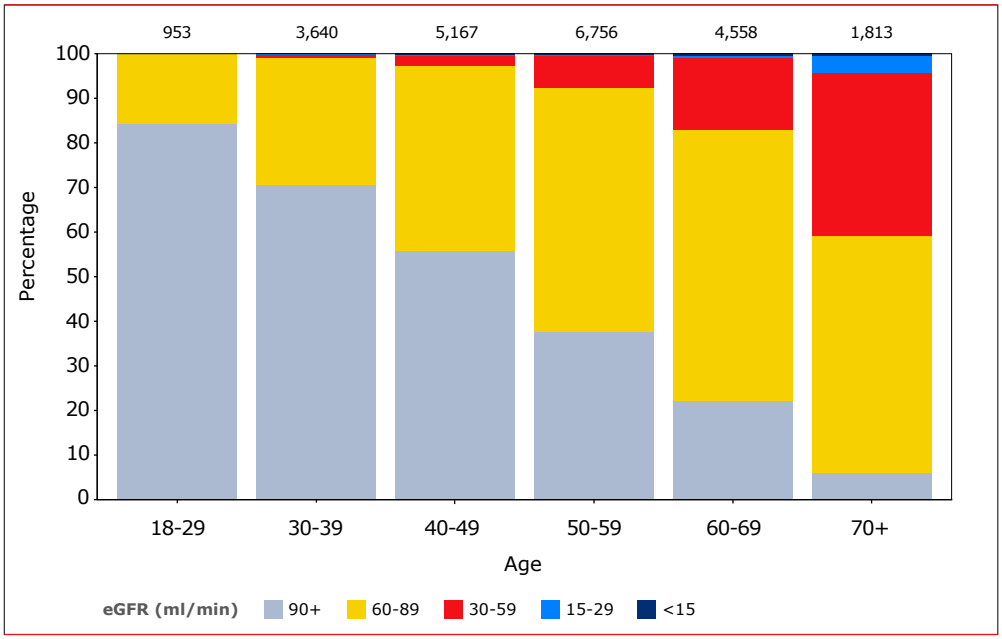
Legend: *eGFR = estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60–89 ml/min/1.73m²: mildly reduced; 30–59 ml/min/1.73m²: moderately reduced; 15–29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

Table 5.6: Crude chronic kidney disease incidence per 1,000 person years of follow up in 2008–2019, and 2020–2023, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2008–2019	9.9 (9.2–10.5)	1.25 (1.17–1.33)	10.3 (9.0–11.7)	1.33 (1.15–1.51)
2020–2023	10.5 (9.6–11.5)	1 (reference)	11.0 (9.0–13.3)	1 (reference)

**Standardised according to the observed age distribution in 2020–2023.*
***Legend:** CI = confidence interval; PYFU = person years.*

Figure 5.6: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2023 for different age categories. For each individual, the last available measurement in 2023 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 2023, 2,462 diagnoses of non-AIDS-defining malignancies in 2,259 unique individuals were recorded in SHM's database. An additional 1,022 patients were diagnosed with one or more non-melanoma skin cancers, but these were not included in the present analysis. *Table 5.7* shows the most common types of non-AIDS-defining cancer:

- lung cancer (16.4%);
- intestinal cancer (mainly oesophageal, gastric, intestinal, and rectal cancers, but excluding hepato-cellular carcinoma and cancer of gallbladder and biliary tract, 13.0%);
- invasive anal cancer (excluding pre-malignant AIN, 11.7%);
- haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 11.2%);
- prostate cancer (11.2%); and
- head and neck cancers (8.3%).

Figure 5.7 shows the changes in types of non-AIDS-defining cancers over time. The proportion of individuals with intestinal, prostate, and renal cancer has increased over time, likely reflecting the increasing age of the study population. This is further illustrated in *Figure 5.8*, which shows the distribution of non-AIDS-defining malignancies with increasing age at cancer diagnosis.

Risk factors for non-AIDS-defining malignancies

The crude incidence of non-AIDS-defining malignancies (NADM) in men and women is shown in *Figure 5.3D*. The age-standardised incidence in men statistically significantly decreased over time (*Table 5.8A*). This lower age-standardised incidence in men may be due to a reduction over time in risk factors such as smoking, and a higher proportion of individuals living with high CD4 cell counts. The temporal trend for women was similar – the age-standardised incidence decreased (although not significantly) over time (*Table 5.8A*).

Demographic and clinical factors independently associated with an increased risk of a first non-AIDS-defining malignancy were (*Appendix Table 5.5*):

- older age group;
- people born in the Netherlands, and migrants from Western countries;
- low body mass index;
- lower current CD4 cell count (CD4 below 350 cells/mm^3);
- prior AIDS;
- chronic HBV co-infection; and
- current or past smoking.

Furthermore, people who had been pre-treated with mono or dual-NRTI-based regimes prior to starting ART had an independently increased risk for NADM, compared with those who were therapy-naïve prior to starting ART (relative risk [RR] 1.19, 95% CI 1.04-1.35). Of note, independent of all other risk factors investigated, people who initiated ART within 12 months of their last negative HIV test had a borderline significant lower risk for NADM (RR 0.77, 95% CI 0.57-1.05) than other therapy-naïve people who started ART (i.e. those who either had an unknown duration of HIV infection, or a duration of more than 12 months).

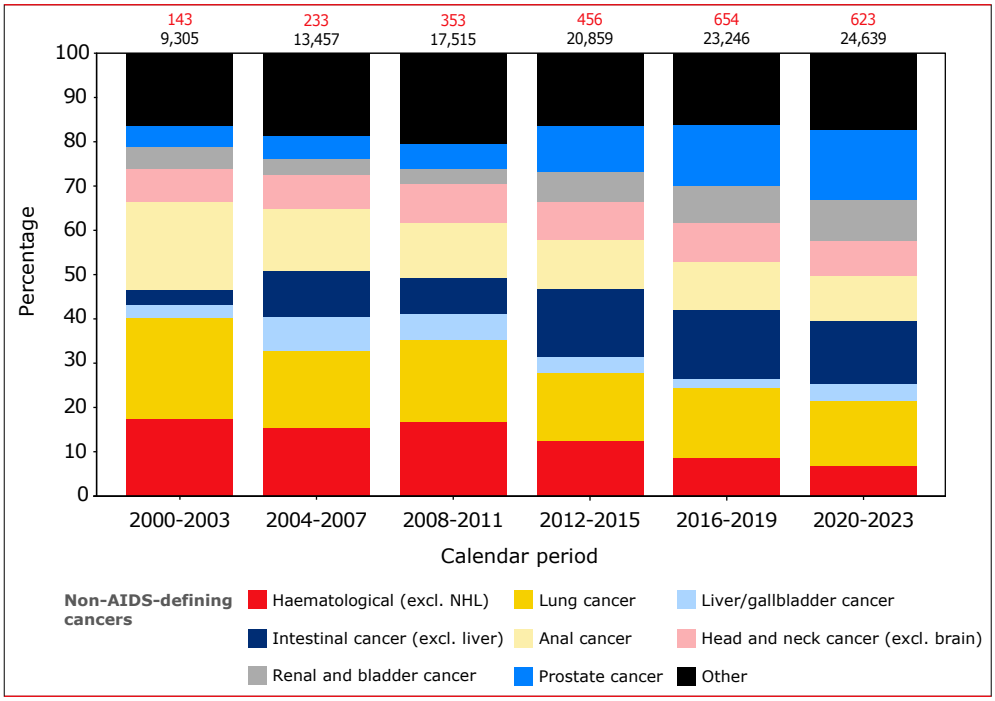
In the period from 1 January 2000 to 31 December 2023, the overall five-year survival rate following the most common non-AIDS-defining malignancies are shown in *Table 5.7* and *Appendix Figure 5.1.* Table 5.7 also shows the distribution and crude 5-year survival rates of the sub-group of NADM diagnosed in the last 10 years of follow-up. The crude 5-year survival rates of liver cancer improved substantially from 19.1% in the period 2000-2023, to 38.8% in the 10-year period 2014-2023, however because of low numbers the uncertainty of this latter estimate is high. For nearly all other NADM we observed no clinically significant change in the crude 5-year survival rates (but with slightly improved survival for lung cancer and malignant melanoma).

We calculated the age- and sex-stratified incidence of non-AIDS-defining malignancy (including non-melanoma skin cancer) per 1,000 person years of follow up in the period 2015-2023, and compared with the incidence in the general Dutch population in 2023 (*Table* & *Figure 5.8B*). The incidence of NADM in all age groups (with at least 15 events) in men was significantly higher than the observed cancer incidence in the general Dutch male population. The relatively low cumulative follow-up time and number of events per age-group in women limits the statistical power of the analysis. However, the observed incidence in each age group appears to be rather similar to the observed cancer incidence in the general Dutch female population.

Anal cancer

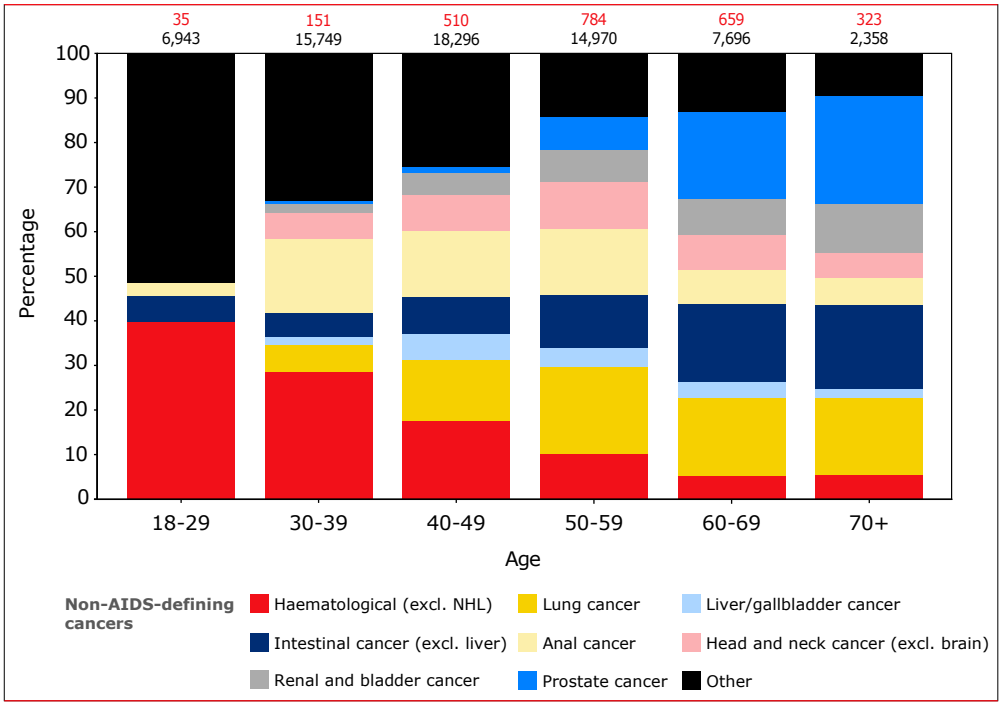
In total, 276 men with HIV and 11 women with HIV were diagnosed with anal cancer. Among men with HIV, the incidence of anal cancer fluctuated between 0.3 and 1.5 cases per 1,000 PYFU between 2000 and 2023 (*Figure 5.3G*). A 2023 study examined trends in incidence of and mortality after anal cancer diagnosis in people living with HIV, including the effect of AIN/anal cancer screening from 2007 onwards, in the Netherlands [52]. It found that anal cancer incidence slowly declined in MSM but not in non-MSM and women, and also that men diagnosed with anal cancer during screening had improved survival compared to those that were diagnosed while not participating in a screening program, probably because they were diagnosed at an earlier disease stage.

Figure 5.7: *Relative changes in non-AIDS-defining malignancies between 2000 and 2023 in PWH in the Netherlands. The numbers at the top of each bar represent the number of non-AIDS-defining cancer diagnoses (top number) and the total number of individuals in care during that calendar period (bottom number).*



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

Figure 5.8: Relative changes in non-AIDS-defining malignancies with increasing age in PWH with HIV in the Netherlands. The numbers at the top of each bar represent the number of individuals at risk and the number of cancer diagnoses in that age category between 2000 and 2023.



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

Table 5.7: Most common non-AIDS-defining malignancies diagnosed in 2000-2023, and a sub-group diagnosed in the last 10 year between 2014-2023, excluding non-melanoma skin cancer and pre-malignant lesions found by cervical and anal screening.

	2000-2023			2014-2023		
Non-AIDS malignancy	**# of malignancies**	**%**	**Five-year survival (%)**	**# of malignancies**	**%**	**Five-year survival (%)**
Lung cancer	403	16.4	16.1	229	15.0	21.6
Intestinal cancer (excl. liver/gallbladder)	321	13.0	32.1	231	15.2	31.6
Anal cancer	287	11.7	66.7	161	10.6	68.4
Hematological (excl. NHL)	276	11.2	64.1	132	8.7	65.6
Prostate cancer	275	11.2	79.7	218	14.3	80.3
Head and neck cancer (excl. brain)	205	8.3	56.7	124	8.1	58.9
Renal and bladder cancer	172	7.0	62.8	131	8.6	60.8
Other cancers	125	5.1	42.5	72	4.7	41.3
Malignant melanoma	114	4.6	77.9	67	4.4	85.3
Liver/gallbladder cancer	98	4.0	15.6	47	3.1	23.0
Breast cancer	70	2.8	75.7	41	2.7	67.8
Testicular cancer	47	1.9	90.1	23	1.5	89.7
Gynecological cancer (excl. cervical)	36	1.5	71.1	19	1.2	69.6
CNS cancer	33	1.3	60.3	27	1.8	50.2

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

Table 5.8A: Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up in 2000-2009, 2010-2019, and 2020-2023, and age-standardised incidence ratio with 95% confidence intervals.

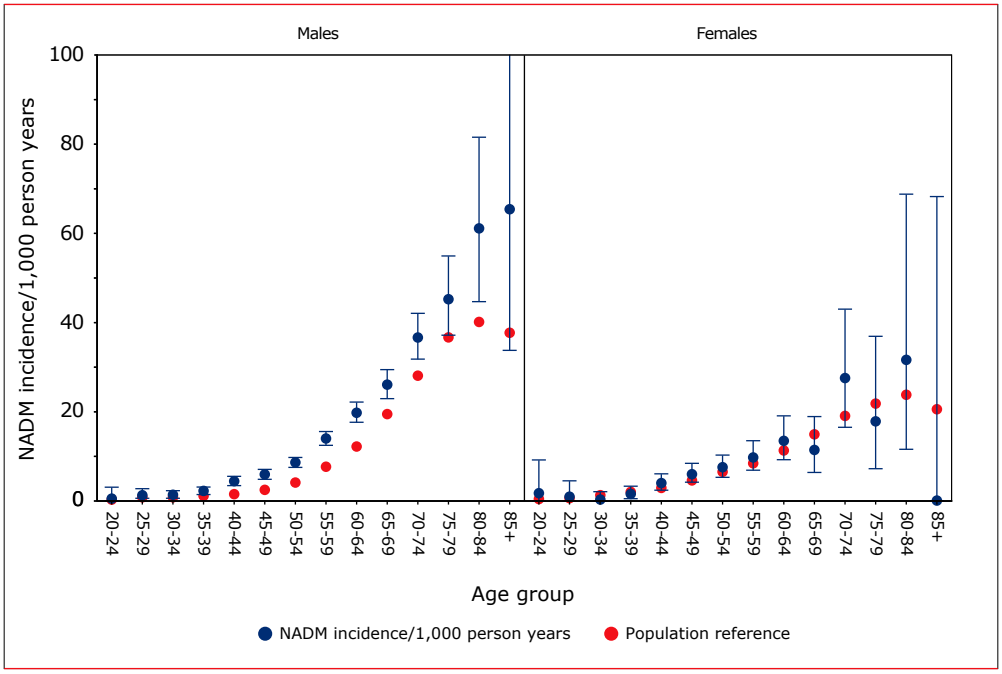
Calendar year	**Male**		**Female**	
	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2000-2009	6.4 (5.9-7.0)	1.64 (1.49-1.78)	3.1 (2.4-4.0)	1.29 (0.97-1.61)
2010-2019	7.5 (7.1-8.0)	1.29 (1.22-1.37)	4.5 (3.8-5.2)	1.10 (0.93-1.27)
2020-2023	7.7 (7.0-8.4)	1 (reference)	5.5 (4.4-6.8)	1 (reference)

**Standardised according to the observed age distribution in 2020-2023.*

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

Table & Figure 5.8B: Age- and sex-stratified incidence of non-AIDS-defining malignancy (including non-melanoma skin cancer) per 1,000 person years of follow up in 2015-2023, compared to the incidence in the general Dutch population in 2023.

Age categories	Males				Females			
	Person-years of follow-up	Number of NADM	Incidence/ 1000PY (95%CI)	Incidence general population	Person-years of follow-up	Number of NADM	Incidence/ 1000PY (95%CI)	Incidence general population
20-24	1782	1	0.6 (0.0-3.1)	0.33	603	1	1.7 (0.0-9.2)	0.31
25-29	6241	9	1.4 (0.7-2.7)	0.62	1237	1	0.8 (0.0-4.5)	0.61
30-34	10776	15	1.4 (0.8-2.3)	0.79	2766	1	0.4 (0.0-2.0)	1.34
35-39	13401	30	2.2 (1.5-3.2)	1.07	4359	7	1.6 (0.6-3.3)	2.09
40-44	16309	72	4.4 (3.5-5.6)	1.52	5306	21	4.0 (2.4-6.0)	3.01
45-49	20514	122	5.9 (4.9-7.1)	2.48	5745	35	6.1 (4.2-8.5)	4.58
50-54	24895	214	8.6 (7.5-9.8)	4.23	5076	38	7.5 (5.3-10.3)	6.48
55-59	22854	319	14.0 (12.5-15.6)	7.71	3780	37	9.8 (6.9-13.5)	8.33
60-64	15693	311	19.8 (17.7-22.1)	12.27	2368	32	13.5 (9.2-19.1)	11.33
65-69	9738	254	26.1 (23.0-29.5)	19.58	1307	15	11.5 (6.4-18.9)	14.94
70-74	5567	204	36.6 (31.8-42.0)	28.12	689	19	27.6 (16.6-43.0)	19.04
75-79	2357	107	45.4 (37.2-54.9)	36.59	391	7	17.9 (7.2-36.9)	21.83
80-84	753	46	61.1 (44.7-81.5)	40.14	190	6	31.6 (11.6-68.8)	23.83
85+	184	12	65.4 (33.8-114)	37.65	54	0	0.0 (0.0-68.3)	20.69



Multimorbidity

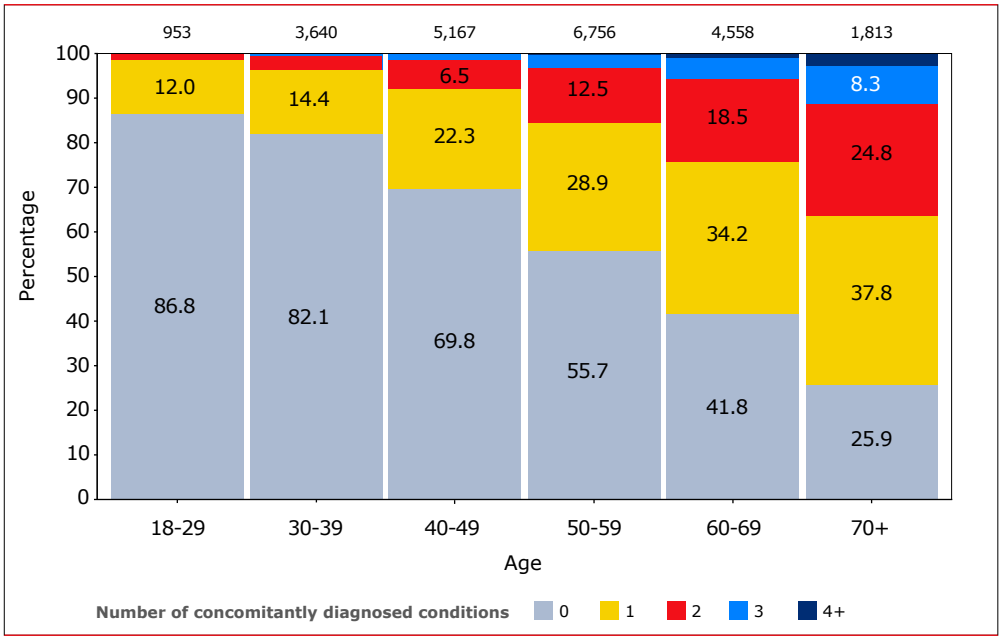
We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infections and AIDS diagnoses did not contribute to the multimorbidity count. The following comorbidities and conditions were taken into account:

1. **Cardiovascular disease** (either myocardial infarction, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy)
2. **Stroke**
3. **Non-AIDS-defining malignancies**, excluding non-melanoma skin cancers and pre-malignant lesions found at cervical/anal screening
4. **Chronic kidney disease** (eGFR below 30 ml/min/1.73 m^2)
5. **Diabetes mellitus** (according to D:A:D diagnostic criteria)
6. **Hypertension**, defined as the use of antihypertensive drugs and/or measured grade 2 (or higher) hypertension with systolic pressure at or above 60 mmHg and/or diastolic pressure at or above 100 mmHg
7. **Obesity** (BMI over 30).

Note that more stringent definitions of CKD and hypertension have been applied here than in the analyses presented earlier in this chapter; this is to avoid overdiagnosis of CKD in people using antiretroviral drugs that inhibit tubular secretion of creatinine, and hypertension in those with borderline hypertension. Recurrences and non-primary CVD, stroke, and non-AIDS-defining malignancy events were not considered. Finally, CKD, hypertension, and obesity could be reversible.

Appendix Figure 5.2 shows the prevalence of each individual comorbidity over calendar time. *Figure 5.9* shows the distribution of the number of concomitantly-diagnosed conditions in various age categories of the adult population in 2023. The number of concomitant conditions was slightly higher in women than in men for all age categories (*Appendix Figure 5.3*). After adjusting for the variables listed in *Appendix Table 5.2*, multimorbidity was independently associated with increased risk of mortality (RR 2.05, 95% CI 1.97-2.12, p<0.001, per additional comorbidity diagnosed).

Figure 5.9: *Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2023. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.*



Polypharmacy

Polypharmacy, commonly defined as the concomitant use of five or more medications, is associated with adverse health outcomes, prescription errors, lower adherence and an increased risk of clinically relevant pharmacological interactions and adverse drug reactions, especially in the elderly. At the end of each calendar year, we count the number of registered comedications for each individual in active follow up. Antiretroviral drugs are excluded from this count. We further excluded the ATC categories "Vitamins (A11)" and "Mineral supplements (A12)" for the count. We counted individual ATC codes (Anatomical Therapeutic Chemical classification systema) of the comedications. Note that coformulated combinations, such as cotrimoxazole, have a single ATC code and therefore increase the comedication count by one.

In 2023, 27.7% of adults in active follow up had no recorded comedication use, 26.8% used one comedication, 14.3% used two comedications, 8.9% used three comedications, and 6.2% used four comedications. A further 16.0% used five or more non-antiretroviral comedications in addition to their ART regimen, which qualifies as polypharmacy.

The prevalence of polypharmacy among adults has increased over time (*Figure 5.10*): in 2000, just 3.3% of adults used five or more non-antiretroviral comedications in addition to their ART regimen. The main drivers for this increase are the rising age of the population and the growth in the number of chronic comorbidities. Older people (*Figure 5.11*) used more comedications, primarily because they have been diagnosed with a higher number of comorbidities. There were some differences between men and women, with women using slightly more comedications than men, while the most pronounced differences were to be found in the youngest age groups. Finally, in adults receiving ART in the period 2007-2023, polypharmacy was also associated with an increased risk of death (RR 2.30, 95% CI 2.09-2.53, $p<0.001$) 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 with HIV in care in 2023 are listed in *Table 5.9*.

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

Table 5.9: Use of comedications in 2023.

Comedication use in 2023	N	%
ATC group		
Vitamins	6805	11.5
Lipid modifying agents	5155	8.7
Drugs for acid related disorders	4145	7.0
Agents acting on the renin-angiotensin system	3699	6.3
Psycholeptics drugs (antipsychotics, anxiolytics, hypnotics, sedatives)	3583	6.1
Antithrombotic agents	3106	5.3
Drugs for obstructive airway diseases	3050	5.2
Drugs used in diabetes	2568	4.3
Psychoanaleptics (antidepressants, psychostimulants)	2495	4.2
Mineral supplements	2042	3.5
Urological drugs	1906	3.2
Beta blocking agents	1765	3.0
Calcium channel blockers	1759	3.0
Antianemic drugs	1338	2.3
Antibacterial drugs	1291	2.2
Diuretic drugs	1265	2.1
Sex hormones and modulators of the genital system	1195	2.0
Corticosteroids systemic	1106	1.9
Topical dermatological corticosteroids	1083	1.8
Analgesic drugs	894	1.5
Antiepileptic drugs	885	1.5
Cardiac therapy	840	1.4
Nasal preparations	789	1.3
Antiviral drugs	745	1.3
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	551	0.9
Antimycotic drugs	531	0.9
Drugs affecting bone structure and mineralization	486	0.8
Immunosuppressants drugs	387	0.7
Thyroid therapy	383	0.6
Ophthalmological drugs	348	0.6
Other nervous system drugs	258	0.4
Anti-inflammatory and antirheumatic drugs	253	0.4

Figure 5.10: 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.

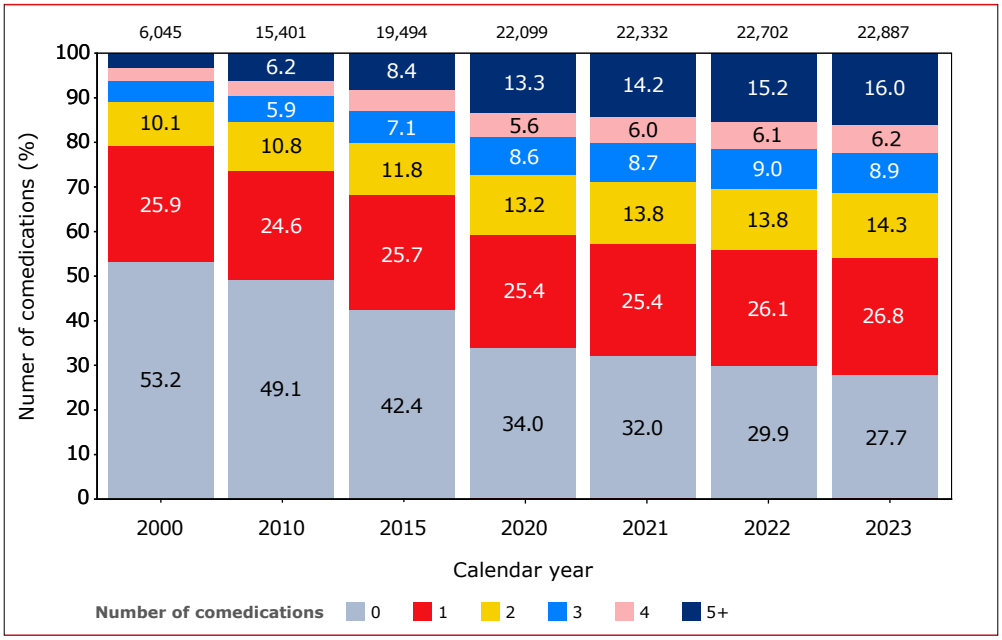
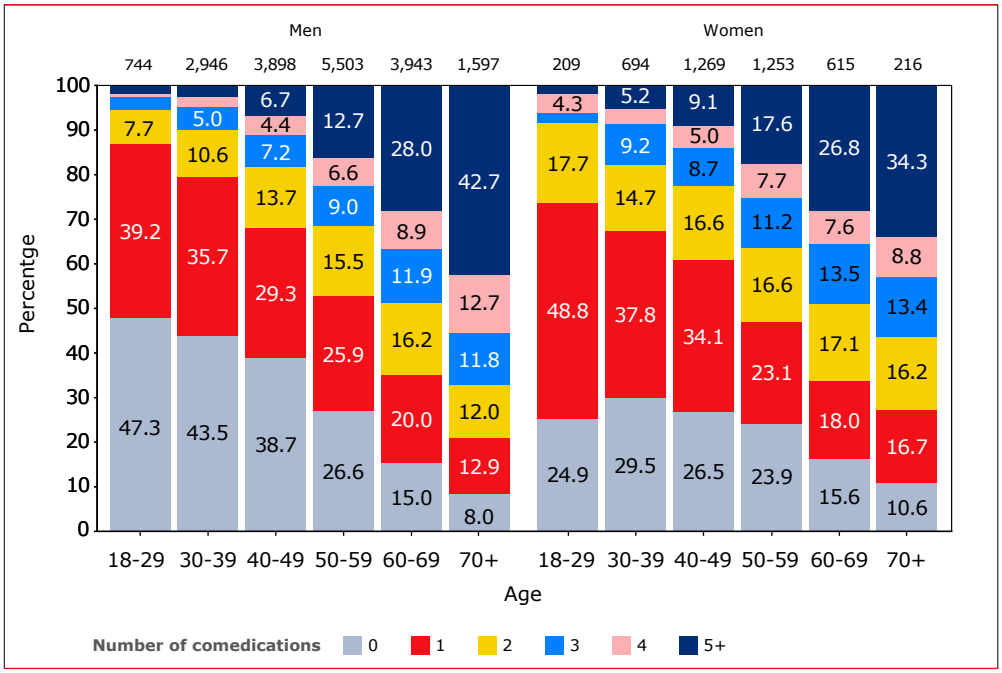


Figure 5.11: Number of comedications used by age group and gender in 2023. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



SARS-CoV-2 and COVID-19

In a recent study, we described the incidence, risk factors, and outcomes of COVID-19 in PWH in the Netherlands using data collected up to 31 December 2021. We found that risk of severe COVID-19 outcomes was increased in individuals with uncontrolled HIV replication, low CD4 count and prior AIDS diagnosis, independent of general risk factors like higher age, comorbidity burden and migrants originating from non-Western countries[53]. Here we present an updated analysis of the incidence, and outcomes of COVID-19 in people living with HIV in the Netherlands using data collected up to 31 December 2023.

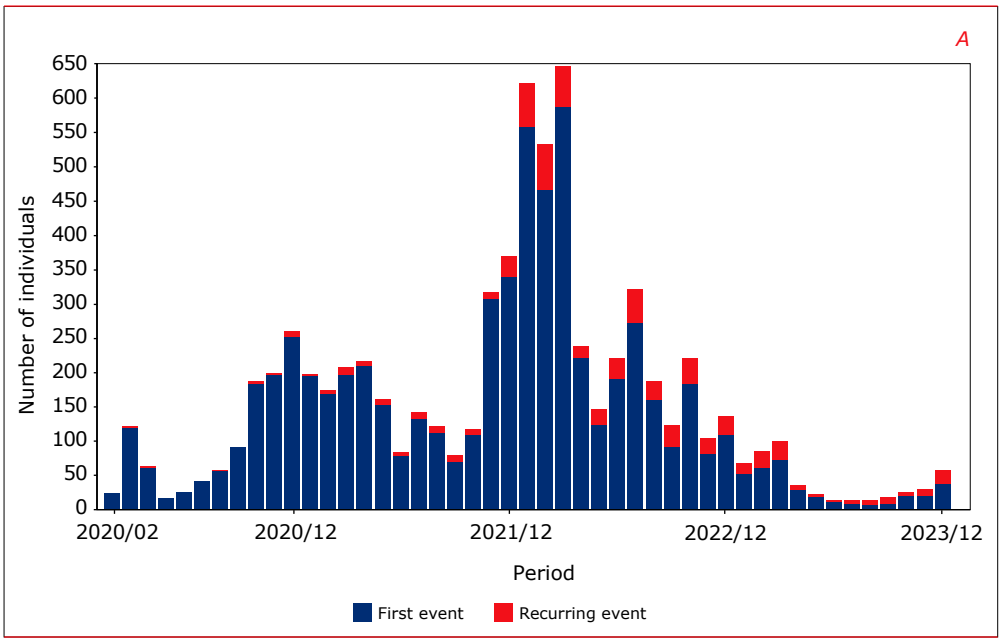
Stichting HIV Monitoring (SHM) records diagnosis of, and hospitalisations for COVID-19, using information available in the electronic medical records (EMRs) of the HIV treatment centers. SHM has not established links to other COVID-19 care providers and cohorts / datasets, nor to SARS-CoV-2 vaccination data repositories. Objective measures of COVID-19 disease severity could often not be recorded by

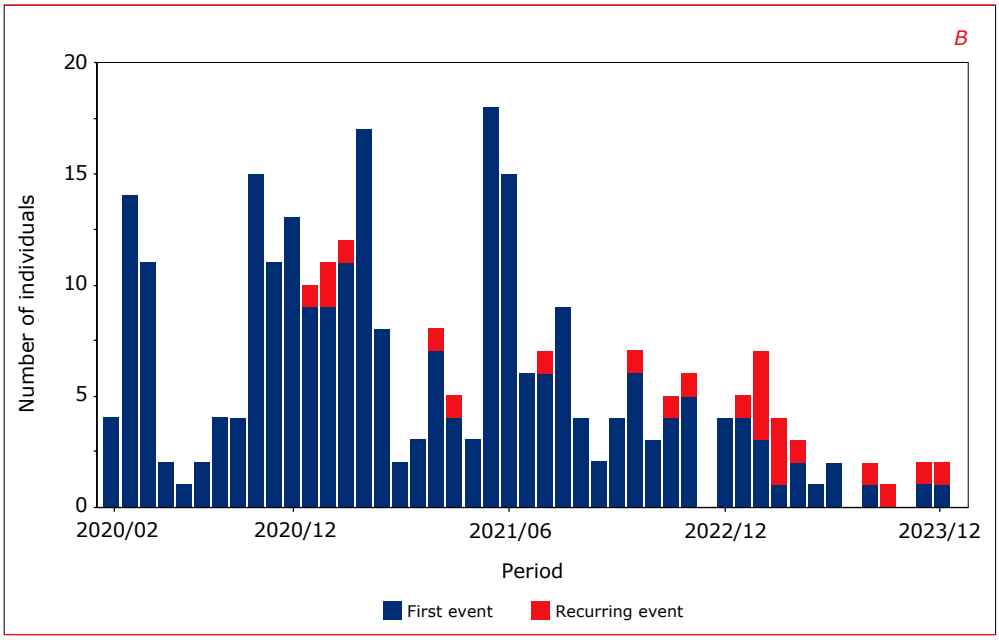
SHM, as these data were not systematically recorded in EMRs, especially for people who weren't hospitalised. In addition, detailed information on COVID-19 disease severity was often not available for patients who had been hospitalised for COVID-19, if the hospital differed from the one in which they received their HIV care. Therefore, we used data on hospitalisation for COVID-19 as a proxy for COVID-19 disease severity.

SHM has collected data on 7,183 COVID-19 events diagnosed between 1 February 2020 and 31 December 2023 in 6,462 individuals (Figure 5.12.A). There were 1,047 COVID-19 events recorded in 2020, 2,055 in 2021, 3,468 in 2022, and only 463 in 2023 (for 150 COVID-19 events no exact date was recorded). A total of 721 COVID-19 events occurred in individuals who had previously been diagnosed with COVID-19. Of the 7,183 recorded COVID-19 events, 279 (3.9%) resulted in hospitalisation (Figure 5.12.B); 46 (0.6%) of which required ICU admission. There were 81 hospitalizations in 2020, 111 in 2021, 58 in 2022, and just 29 in 2023. Table 5.10 describes the characteristics of the individuals that were diagnosed with (or hospitalized for) COVID-19, with individuals that had multiple COVID-19 events contributing only one (the most severe) event. The characteristics of the overall population living with HIV in care in the Netherlands in 2022 (the year in which the largest number of COVID-19 diagnoses were recorded) is also described in *Table 5.10*. Compared to the total population living with HIV, those who were hospitalised for COVID-19 were older, were more likely to have acquired HIV through heterosexual contact (both men and women), and were more likely to be born in sub-Saharan Africa or Latin America (including the Caribbean). Overall, men were not more likely than women to be diagnosed with or hospitalised for COVID-19; however, MSM were much less likely while the other (mostly heterosexual) men were more likely.
Regarding HIV-related characteristics, there were only minor differences between people living with HIV who were diagnosed with COVID-19, and the total population living with HIV, with the overwhelming majority being on ART, with a plasma HIV-1 viral load below 200 cps/mL, and a high median CD4 cell count well above 500 cells/mm^3. There were, however, noticeable differences between people diagnosed with COVID-19 who were hospitalised and those who weren't hospitalised; for example, the former had generally been HIV-positive for longer, but this is most likely driven by the fact that those who were hospitalised were on average eight years older. Furthermore, those who were hospitalised had lower current and nadir CD4 cell counts, and had more frequently had a prior AIDS diagnosis, compared to those not hospitalised (*Table 5.10*).
The bottom half of *Table 5.10* shows the distribution of selected comorbidities among individuals diagnosed with COVID-19. All investigated comorbidities were much more prevalent among the group that was hospitalised, resulting in a higher total multimorbidity count in the hospitalised group.

In total, 45 (0.63%) of the 6,462 individuals diagnosed with one (or more) COVID-19 event(s) were reported to have died as a direct result of COVID-19 (Figure 5.12.C). There were 13 COVID-19-related deaths recorded in 2020, 21 in 2021, 9 in 2022, and just 2 in 2023.

Figure 5.12.A-C: *Incidence of COVID-19 diagnoses (A), hospitalizations (B) and deaths (C) over calendar time.*




B
20
15
10
5
0
Number of individuals
2020/02
2020/12
2021/06
2022/12
2023/12
Period
First event
Recurring event

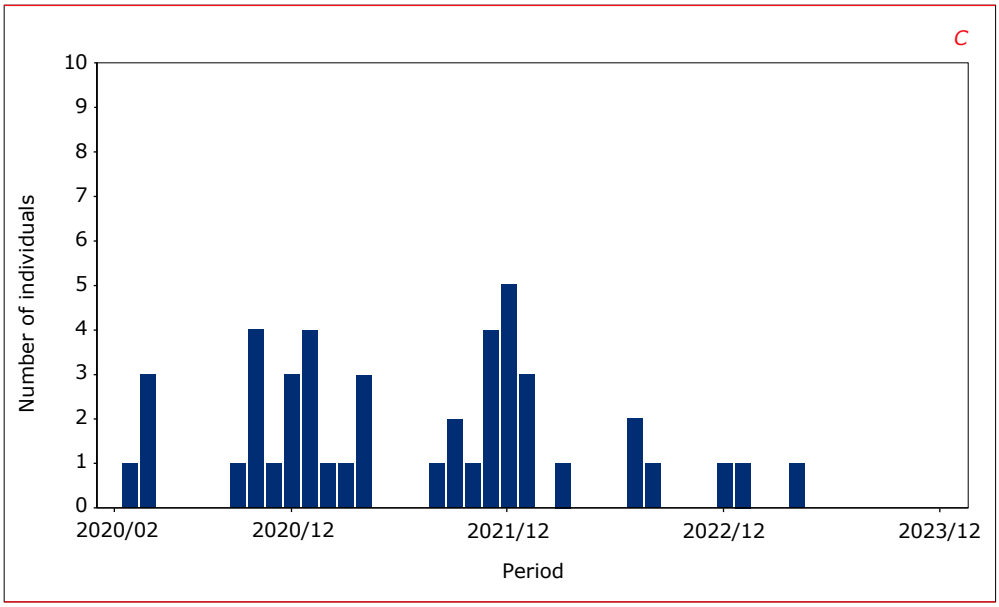

C
10
9
8
7
6
5
4
3
2
1
0
Number of individuals
2020/02
2020/12
2021/12
2022/12
2023/12
Period

Table 5.10: Characteristics of individuals diagnosed with COVID-19.

	All PWH in 2022	Hospitalised	Not hospitalised
N	**21,901**	**268**	**6,194**
Age, years	51.1 (41.3-59.0)	59.8 (51.3-66.6)	49.9 (39.5-58.4)
Male sex	81.8%	79.1%	81.9%
HIV transmission category			
MSM	63.5%	42.9%	66.5%
Other men	18.3%	36.25	15.5%
Women	18.2%	20.9%	18.1%
Region of origin			
Netherlands / Europe / North America	69.8%	55.6%	64.8%
Sub-Saharan Africa	12.1%	16.0%	8.8%
Latin America / Caribbean	12.9%	17.2%	12.8%
Other regions	5.3%	11.2%	13.6%
Years known to be HIV positive	12.5 (7.2-18.6)	15.5 (8.4-21.9)	12.3 (6.7-18.5
On ART	97.3%	96.1%	98.9%
HIV viral load >200 cps/mL	3.3%	8.5%	2.2%
Current CD4 count, mm^3	690 (507-905)	550 (350-790)	710 (530-920)
Nadir CD4 count, mm^3	250 (120-385)	159 (50-270)	262 (136-410)
Prior AIDS diagnosis	22.3%	38.8%	18.9%
Comorbidities			
Obesity (BMI>30 kg/m^2)	12.4%	25.2%	14.1%
Diabetes mellitus type 2	5.2%	23.3%	5.4%
Cardiovascular disease	3.6%	12.4%	3.9%
Stroke	1.8%	7.4%	2.1%
Hypertension (grade 2+ or on medication)	13.4%	32.2%	16.0%
Non-AIDS-defining malignancy	3.5%	10.5%	4.1%
Chronic kidney disease (eGFR<60 ml/min)	0.8%	7.8%	0.8%
Multimorbidity count			
0	62.2%	38.0%	65.9%
1	24.5%	25.2%	24.5%
2	9.9%	20.5%	7.3%
3 or more	3.4%	16.3%	2.2%

Legend: *N (%) or median (IQR), as appropriate; MSM = men who have sex with men; cps/ml = copies per millilitre; ART = antiretroviral therapy. BMI=body mass index; eGFR=estimated glomerular filtration rate in millilitres per minute.*

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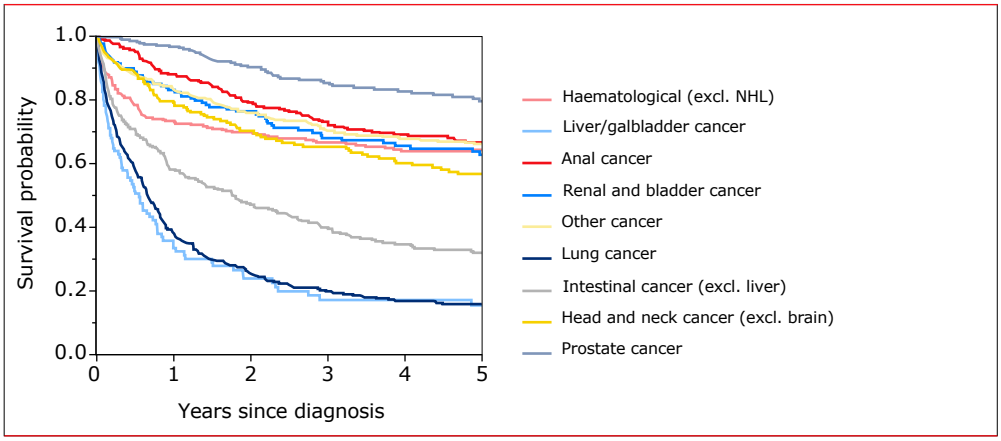
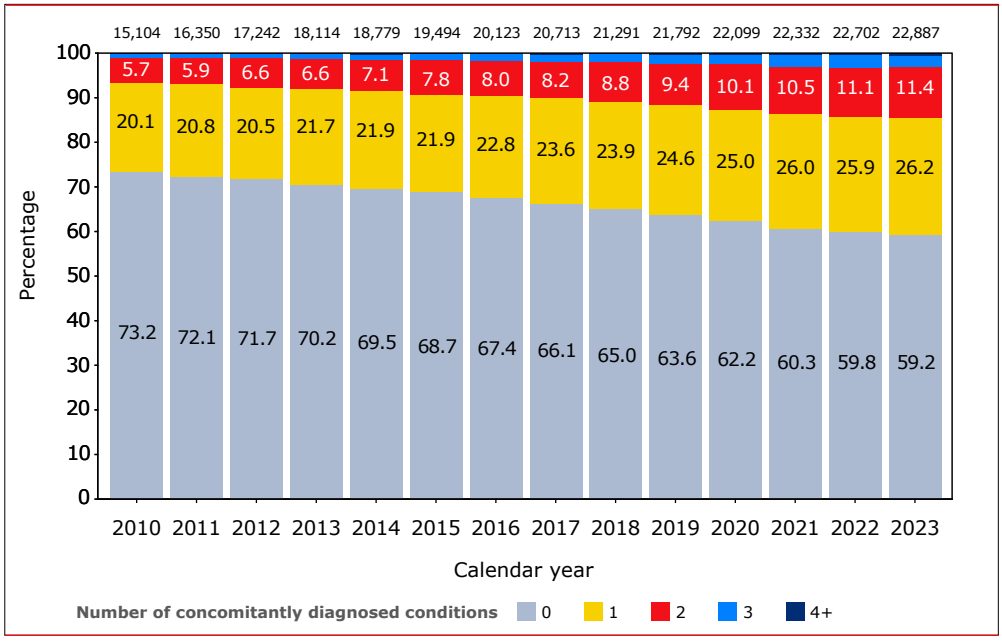
Appendix: supplementary figures and tables

Appendix Figure 5.1: *Estimated five-year survival following the diagnosis of the most common non-AIDS-defining malignancies diagnosed between 1 January 2000 and 31 December 2023.*

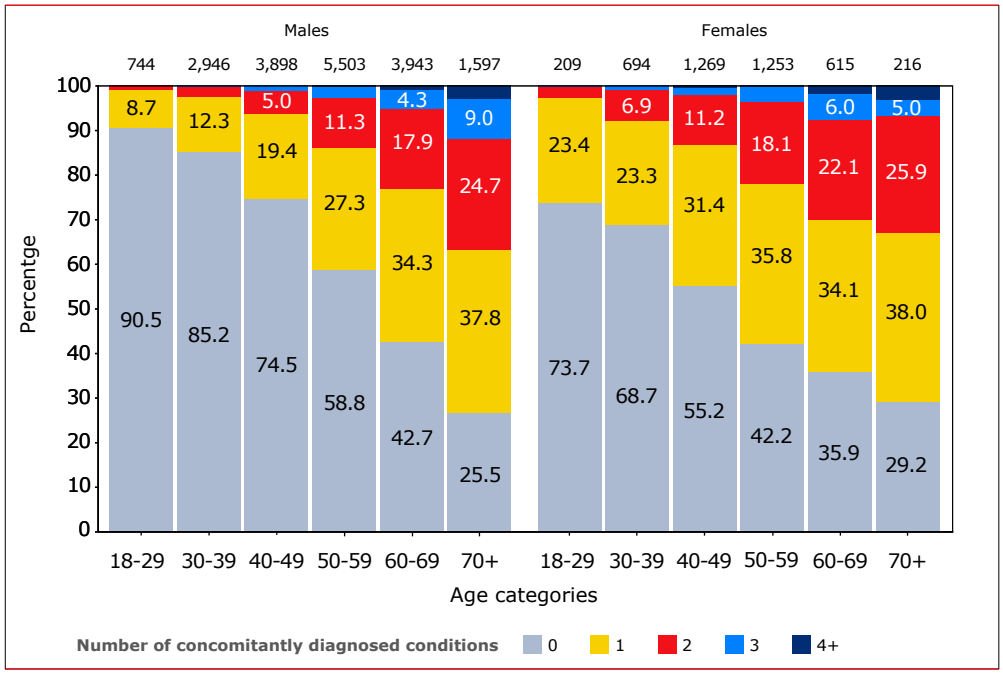


Legend: *KM = Kaplan-Meier; excl. = excluding; NHL = non-Hodgkin's lymphoma.*

Appendix Figure 5.2: *Prevalence of non-AIDS multimorbidity in the adult population. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per calendar year.*



Appendix Figure 5.3: *Prevalence of non-AIDS multimorbidity by gender in the adult population in 2023. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.*



Appendix Table 5.1: *Absolute number of causes of death among PWH during the periods 1996–2023.*

	Calendar period									
Causes of death	**96–99**	**00–04**	**05–09**	**10–14**	**15–19**	**20–23**	**2020**	**2021**	**2022**	**2023**
1. AIDS										
1.1 AIDS – infection	58	90	169	118	31	25	5	3	5	12
1.2 AIDS – malignancy	52	53	71	45	56	38	6	9	14	9
1.3 AIDS – unclassifiable	79	72	14	10	28	14	4	4	2	4
Subtotal	*189*	*215*	*254*	*173*	*115*	*77*	*15*	*16*	*21*	*25*
2. Non-AIDS malignancies	21	79	132	182	275	259	70	70	56	63
3. Cardiovascular disease										
3.1 Myocardial infarction	9	31	28	31	28	44	14	13	8	9
3.2 Stroke	2	10	9	14	18	23	3	7	10	3
3.3 Other CVD	4	20	42	50	68	75	11	16	20	28
Subtotal	*15*	*61*	*79*	*95*	*114*	*142*	*28*	*36*	*38*	*40*
4. Non-AIDS infection	19	45	29	24	33	70	16	30	12	12
5. Liver disease	10	22	54	48	27	14	2	4	4	4
6. Lung disease	4	13	24	30	67	40	7	11	10	12
7. Non-natural death										
7.1 Accident or violence	5	11	22	17	16	17	2	4	5	6
7.2 Suicide	9	23	35	45	53	36	14	8	7	7
7.3 Euthanasia	4	8	.	2	1	.	.	.	.	.
Subtotal	*18*	*42*	*57*	*64*	*70*	*53*	*16*	*12*	*12*	*13*
8. Alcohol and substance use	8	15	25	23	22	25	4	7	8	6
9. Other causes	11	29	26	38	57	78	15	22	19	22
10. Unknown	18	50	53	71	88	112	24	26	30	32
Total	**313**	**571**	**733**	**748**	**868**	**870**	**197**	**234**	**210**	**229**

Legend: *CVD = cardiovascular disease.*

Appendix Table 5.2: Adjusted risk factors for death and AIDS among PWH.

	Death			AIDS		
Risk factors	**RR (95%CI)**	**p-value**	**Overall p-value**	**RR (95%CI)**	**p-value**	**Overall p-value**
Region of birth						
Native Dutch	1 (reference)		0.010	1 (reference)		0.128
Western migrants	0.97 (0.85-1.11)	0.669		1.24 (1.04-1.48)	0.015	
Non-Western migrants	0.89 (0.80-0.98)	0.018		1.04 (0.92-1.18)	0.497	
Unknown origin	2.12 (1.20-3.74)	0.010		1.03 (0.53-2.01)	0.935	
HIV-1 transmission route						
MSM	1 (reference)		<.001	1 (reference)		0.264
Other men	1.16 (1.05-1.28)	0.004		0.95 (0.83-1.08)	0.422	
Women	0.89 (0.78-1.01)	0.080		0.93 (0.80-1.07)	0.295	
Transgender	0.85 (0.46-1.59)	0.609		1.24 (0.72-2.16)	0.439	
IDU	1.46 (1.23-1.74)	<.001		0.75 (0.58-0.96)	0.022	
Blood contact	0.83 (0.62-1.11)	0.210		0.82 (0.58-1.17)	0.278	
Pediatric transmission	1.33 (0.63-2.81)	0.449		1.20 (0.63-2.31)	0.576	
Age *						
18-29	0.86 (0.63-1.19)	0.365	<.001	1.07 (0.87-1.32)	0.520	<.001
30-39	1 (reference)			1 (reference)		
40-49	1.58 (1.36-1.83)	<.001		1.07 (0.94-1.21)	0.306	
50-59	2.79 (2.42-3.22)	<.001		1.26 (1.10-1.45)	0.001	
60-69	4.99 (4.29-5.79)	<.001		1.29 (1.08-1.54)	0.005	
70+	12.24 (10.41-14.39)	<.001		1.83 (1.42-2.36)	<.001	
CD4 cell count **						
0-50	11.04 (9.30-13.09)	<.001	<.001	7.27 (5.92-8.94)	<.001	<.001
50-199	4.50 (3.98-5.09)	<.001		2.87 (2.46-3.35)	<.001	
200-349	2.03 (1.80-2.28)	<.001		1.56 (1.34-1.82)	<.001	
350-499	1.38 (1.23-1.55)	<.001		1.23 (1.05-1.43)	0.008	
500-749	1 (reference)			1 (reference)		
750+	0.87 (0.77-0.99)	0.030		1.08 (0.91-1.28)	0.359	
Per year longer on cART with HIV RNA>1000 cp/mL	1.05 (1.04-1.07)	<.001	<.001	1.04 (1.02-1.07)	<.001	<.001
Treatment status						
Treatment-experienced at start cART	0.94 (0.86-1.03)	0.188		0.63 (0.56-0.72)	<.001	
Treatment-naive at start	1 (reference)			1 (reference)		
Prior AIDS event	1.65 (1.52-1.78)	<.001				
Hepatitis B virus positive	1.25 (1.10-1.41)	<.001		1.04 (0.86-1.24)	0.706	

			Death			AIDS
Risk factors	**RR (95%CI)**	**p-value**	**Overall p-value**	**RR (95%CI)**	**p-value**	**Overall p-value**
Hepatitis C virus positive	1.55 (1.36-1.77)	<.001		1.22 (1.01-1.46)	0.037	
Body mass index *						
<18	3.11 (2.77-3.50)	<.001	<.001			
18-25	1 (reference)					
25-30	0.68 (0.62-0.75)	<.001				
30+	0.84 (0.73-0.97)	0.018				
Smoking status						
Current smoker	1.22 (1.09-1.37)	<.001	<.001	0.75 (0.66-0.84)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	1.97 (1.78-2.18)	<.001		0.94 (0.82-1.07)	0.334	
Early cART ***	0.82 (0.62-1.08)	0.159		1.21 (0.93-1.58)	0.150	

**Time-updated.*

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

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

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

***Appendix Table 5.3:** Lost to care (no follow up after 31 December 2021) by region of origin and time-updated CD4 cell count.*

		Total population			Native Dutch			Western migrants			non-Western migrants		
Last CD4 count	**N**	**PY**	**Incidence/ 1000PY (95%CI)**	**N**	**PY**	**Incidence/ 1000PY (95%CI)**	**N**	**PY**	**Incidence/ 1000PY (95%CI)**	**N**	**PY**	**Incidence/ 1000PY (95%CI)**
0-50	73	3,479	21.0 (16.4-26.4)	7	1,975	3.5 (1.4-7.3)	16	310	51.7 (29.5-83.9)	50	1,195	41.8 (31.1-55.2)
050-199	258	12,673	20.4 (17.9-23.0)	33	6,915	4.8 (3.3-6.7)	48	1,444	33.3 (24.5-44.1)	177	4,315	41.0 (35.2-47.5)
200-349	516	27,939	18.5 (16.9-20.1)	84	16,257	5.2 (4.1-6.4)	97	2,139	45.3 (36.8-55.3)	335	9,543	35.1 (31.4-39.1)
350-499	692	53,658	12.9 (12.0-13.9)	122	31,987	3.8 (3.2-4.6)	139	4,433	31.4 (26.4-37.0)	431	17,239	25.0 (22.7-27.5)
500-749	1,042	12,5751	8.3 (7.8-8.8)	246	73,800	3.3 (2.9-3.8)	249	11,003	22.6 (19.9-25.6)	547	40,948	13.4 (12.3-14.5)
750+	790	163,555	4.8 (4.5-5.2)	205	97,445	2.1 (1.8-2.4)	231	17,301	13.4 (11.7-15.2)	354	48,809	7.3 (6.5-8.0)

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

Appendix Table 5.4: *Absolute number of first AIDS events among PWH during the periods 1996–1999, 2000–2004, 2005–2009, 2010–2014, 2015–2019, and 2020–2023.*

CDC event	1996–1999	2000–2004	2005–2009	2010–2014	2015–2019	2020–2023	Total	
	N	N	N	N	N	N	N	%
AIDS dementia complex – HIV encephalopathy	34	40	54	42	25	15	210	2.87
Bacterial pneumonia, recurring	41	53	77	65	109	56	401	5.48
CMV colitis/proctitis	1	.	1	1	4	2	9	0.12
CMV disease	21	33	29	35	8	.	126	1.72
CMV esophagitis	.	.	.	.	.	1	1	0.01
CMV meningo-encefalitis	.	.	.	.	1	.	1	0.01
CMV pneumonitis	.	.	.	.	11	18	29	0.40
CMV retinitis	26	19	16	13	13	1	88	1.20
Candidiasis esophagitis	221	215	274	222	164	109	1205	16.47
Candidiasis lungs/bronchial/trachea	4	13	9	7	5	4	42	0.57
Cervical cancer, invasive	2	6	5	6	5	1	25	0.34
Coccidioimycosis, extrapulmonary / disseminated	.	.	1	.	.	.	1	0.01
Cryptococcosis, extrapulmonary / disseminated	18	29	39	12	15	2	115	1.57
Cryptosporidiosis	18	15	9	14	4	4	64	0.87
Cystoisosporiasis	1	11	5	1	.	.	18	0.25
HIV wasting	43	45	77	77	70	33	345	4.72
HSV chronic ulcer	1	.	4	3	22	27	57	0.78
HSV esophagitis	.	.	.	.	.	1	1	0.01
HSV pneumonitis	.	.	1	.	.	1	2	0.03
Herpes simplex virus	27	33	58	44	15	.	177	2.42
Histoplasmosis, extrapulmonary / disseminated	5	13	12	8	2	1	41	0.56
Kaposi sarcoma	134	131	192	155	97	50	759	10.37
Leishmaniasis visceral	.	1	2	2	1	.	6	0.08
Microsporidiosis	11	1	2	2	.	1	17	0.23
Mycobacterium avium/kansasii, extrapulmonary / disseminated	21	23	23	14	9	1	91	1.24
Mycobacterium avium/kansasii, pulmonary	1	1	1	1	9	5	18	0.25
Mycobacterium other / unspecified, extrapulmonary / disseminated	18	13	8	10	5	1	55	0.75
Mycobacterium other / unspecified, pulmonary	2	2	5	10	4	3	26	0.36
Non-Hodgkin`s lymphoma (NHL)	48	73	96	98	93	43	451	6.16

CDC event	1996–1999	2000–2004	2005–2009	2010–2014	2015–2019	2020–2023	Total	
	N	N	N	N	N	N	N	%
Penicilliosis	.	.	1	.	.	.	1	0.01
Pneumocystis jirovecii extrapulmonary	.	1	3	1	1	1	7	0.10
Pneumocystis jirovecii pneumonia	269	302	315	297	214	130	1527	20.87
Primary CNS lymphoma	5	6	8	7	5	1	32	0.44
Progressive multifocal leukoencephalopathy	14	20	37	27	10	7	115	1.57
Salmonella sepsis, recurring	2	.	.	1	.	.	3	0.04
Toxoplasmosis of the brain	56	93	62	54	32	14	311	4.25
Tuberculosis, extrapulmonary / disseminated	56	112	91	59	38	24	380	5.19
Tuberculosis, pulmonary	80	167	133	93	68	18	559	7.64
Total	**1,180**	**1,471**	**1,650**	**1,381**	**1,059**	**575**	**7,316**	**100.00**

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

Appendix Table 5.5: *Adjusted risk factors for non-AIDS-defining morbidity.*

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
Male gender	1.20 (1.08-1.32)	<.001	.	1.60 (1.34-1.90)	<.001	.
Region of birth						
Netherlands	1 (reference)	.	0.026	1 (reference)	.	0.466
Other	1.08 (1.01-1.16)	0.026	.	0.96 (0.86-1.07)	0.467	.
HIV-1 transmission route						
MSM	1 (reference)	.	<.001	1 (reference)	.	0.021
Heterosexual	1.17 (1.07-1.27)	<.001	.	1.18 (1.03-1.35)	0.014	.
IDU	1.30 (1.08-1.56)	0.005	.	1.21 (0.91-1.61)	0.188	.
Blood contact	1.16 (0.91-1.47)	0.227	.	1.15 (0.79-1.68)	0.458	.
Age *						
18-29	0.64 (0.49-0.83)	<.001	<.001	0.44 (0.23-0.82)	0.010	<.001
30-39	1 (reference)	.	.	1 (reference)	.	.
40-49	2.05 (1.81-2.31)	<.001	.	2.74 (2.17-3.46)	<.001	.
50-59	3.82 (3.38-4.31)	<.001	.	5.94 (4.73-7.46)	<.001	.
60-69	6.50 (5.70-7.41)	<.001	.	9.66 (7.60-12.28)	<.001	.
70+	10.27 (8.76-12.04)	<.001	.	16.21 (12.37-21.24)	<.001	.
CD4 cell count **						
0-50	3.95 (3.14-4.96)	<.001	<.001	2.79 (1.84-4.24)	<.001	<.001
050-199	1.71 (1.48-1.98)	<.001	.	1.42 (1.13-1.80)	0.003	.
200-349	1.23 (1.11-1.37)	<.001	.	1.25 (1.06-1.46)	0.008	.
350-499	1.04 (0.95-1.14)	0.396	.	1.02 (0.88-1.18)	0.789	.
500-749	1 (reference)	.	.	1 (reference)	.	.
750+	1.12 (1.04-1.22)	0.005	.	1.24 (1.10-1.40)	<.001	.
Per year longer with CD4<200 cells/mm^3	1.01 (0.99-1.03)	0.458	.	1.03 (1.00-1.06)	0.044	.
Prior AIDS event	1.21 (1.13-1.29)	<.001	.	1.16 (1.04-1.29)	0.007	.
Per year longer on cART while HIV RNA>1000 cp/mL	1.02 (1.00-1.03)	0.108	.	1.00 (0.97-1.03)	0.919	.
Treatment status						
Not (yet) started cART	1.19 (1.04-1.35)	0.009	<.001	1.06 (0.85-1.33)	0.605	0.031
Treatment-experienced at start cART	1.28 (1.17-1.40)	<.001	.	1.20 (1.05-1.37)	0.008	.
Treatment-naive at start	1 (reference)	.	.	1 (reference)	.	.
Per year longer on cART	1.00 (1.00-1.01)	0.196	.	1.00 (0.99-1.01)	0.995	.
Early cART within 12 months after last HIV-negat	0.80 (0.66-0.98)	0.030	.	1.06 (0.81-1.40)	0.669	.

Non-AIDS-defining malignancy			Diabetes mellitus			CKD		
IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
0.99 (0.84-1.18)	0.929	.	1.21 (1.04-1.40)	0.013	.	0.63 (0.55-0.72)	<.001	.
1 (reference)	.	0.004	1 (reference)	.	<.001	1 (reference)	.	<.001
0.84 (0.75-0.95)	0.004	.	1.53 (1.37-1.71)	<.001	.	0.77 (0.70-0.85)	<.001	.
1 (reference)	.	0.020	1 (reference)	.	<.001	1 (reference)	.	0.028
0.98 (0.85-1.13)	0.782	.	1.39 (1.22-1.60)	<.001	.	0.99 (0.88-1.12)	0.913	.
1.35 (1.02-1.78)	0.035	.	1.50 (1.08-2.07)	0.014	.	1.53 (1.18-1.98)	0.001	.
1.34 (0.95-1.90)	0.099	.	1.43 (1.00-2.04)	0.051	.	1.18 (0.87-1.62)	0.293	.
0.85 (0.53-1.35)	0.482	<.001	0.64 (0.45-0.93)	0.019	<.001	0.34 (0.15-0.74)	0.007	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
2.38 (1.89-3.00)	<.001	.	1.55 (1.30-1.84)	<.001	.	3.05 (2.32-4.02)	<.001	.
4.60 (3.66-5.78)	<.001	.	2.44 (2.04-2.92)	<.001	.	8.53 (6.55-11.12)	<.001	.
9.60 (7.58-12.16)	<.001	.	3.75 (3.07-4.58)	<.001	.	23.18 (17.77-30.24)	<.001	.
16.93 (13.02-22.01)	<.001	.	4.17 (3.18-5.48)	<.001	.	41.00 (30.95-54.30)	<.001	.
3.42 (2.27-5.16)	<.001	<.001	5.79 (4.15-8.06)	<.001	<.001	1.67 (0.94-2.98)	0.083	<.001
1.96 (1.56-2.47)	<.001	.	1.79 (1.42-2.27)	<.001	.	1.58 (1.27-1.97)	<.001	.
1.36 (1.16-1.60)	<.001	.	1.11 (0.93-1.32)	0.255	.	1.19 (1.03-1.38)	0.015	.
1.08 (0.94-1.24)	0.290	.	1.02 (0.88-1.19)	0.779	.	1.04 (0.93-1.17)	0.470	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.92 (0.81-1.05)	0.201	.	1.23 (1.08-1.40)	0.002	.	0.94 (0.85-1.04)	0.234	.
1.00 (0.97-1.02)	0.788	.	1.00 (0.97-1.03)	0.930	.	0.99 (0.97-1.02)	0.515	.
1.14 (1.03-1.28)	0.014	.	1.29 (1.15-1.44)	<.001	.	1.13 (1.04-1.24)	0.006	.
1.00 (0.97-1.03)	0.833	.	0.99 (0.96-1.02)	0.340	.	0.98 (0.95-1.01)	0.127	.
1.23 (0.99-1.53)	0.063	0.023	1.49 (1.21-1.83)	<.001	<.001	0.38 (0.27-0.55)	<.001	<.001
1.17 (1.01-1.34)	0.031	.	1.31 (1.13-1.52)	<.001	.	1.18 (1.04-1.34)	0.012	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.00 (0.99-1.01)	0.659	.	1.01 (1.00-1.02)	0.055	.	0.98 (0.97-0.99)	<.001	.
0.62 (0.43-0.88)	0.008	.	0.63 (0.42-0.94)	0.023	.	0.98 (0.80-1.21)	0.863	.

	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	1.51 (1.26-1.81)	<.001	<.001	1.18 (0.88-1.59)	0.266	0.011
18-25	1 (reference)	.	.	1 (reference)	.	.
25-30	1.23 (1.14-1.32)	<.001	.	1.02 (0.91-1.14)	0.739	.
30+	2.07 (1.89-2.28)	<.001	.	1.25 (1.05-1.47)	0.010	.
Hepatitis B virus positive	1.22 (1.09-1.36)	<.001	.	0.98 (0.81-1.19)	0.844	.
Hepatitis C virus positive	1.05 (0.94-1.18)	0.399	.	1.05 (0.88-1.25)	0.595	.
Hypertension	1.14 (1.07-1.21)	<.001	.	1.23 (1.11-1.35)	<.001	.
Smoking status						
Current smoker	1.37 (1.27-1.48)	<.001	<.001	1.82 (1.61-2.06)	<.001	<.001
Never smoker	1 (reference)	.	.	1 (reference)	.	.
Past smoker	1.38 (1.28-1.50)	<.001	.	1.49 (1.31-1.70)	<.001	.
Calendar year period						
2000-2010	1.28 (1.17-1.40)	<.001	<.001	1.68 (1.43-1.98)	<.001	<.001
2011-2015	1.17 (1.08-1.26)	<.001	.	1.34 (1.16-1.55)	<.001	.
2016-2022	1 (reference)	.	.	1 (reference)	.	.
Recent use of ABC ***		.	.	1.49 (1.33-1.68)	<.001	.
Per year longer on LOP/r		.	.	1.00 (0.99-1.01)	0.425	.
Per year longer on IDV		.	.	1.00 (0.99-1.01)	0.828	.
Current use of bictegravir		.	.	1.24 (0.91-1.67)	0.171	.
Current use of dolutegravir		.	.	1.40 (1.19-1.64)	<.001	.
Current use of elvitegravir		.	.	1.03 (0.81-1.30)	0.828	.
Current use of raltegravir		.	.	1.82 (1.51-2.19)	<.001	.
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 rilpivirine		.	.		.	.

**Time-updated.*

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

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

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

Non-AIDS-defining malignancy			Diabetes mellitus			CKD		
IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
1.96 (1.54-2.49)	<.001	<.001	1.45 (1.01-2.07)	0.045	<.001	1.26 (0.96-1.67)	0.099	0.020
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.90 (0.80-1.02)	0.096	.	2.26 (1.98-2.57)	<.001	.	1.16 (1.06-1.27)	0.002	.
1.00 (0.83-1.21)	0.974	.	5.46 (4.73-6.30)	<.001	.	1.12 (0.98-1.28)	0.101	.
1.63 (1.39-1.92)	<.001	.	1.11 (0.91-1.34)	0.316	.	1.38 (1.18-1.62)	<.001	.
1.08 (0.90-1.29)	0.392	.	0.97 (0.80-1.18)	0.771	.	1.23 (1.07-1.42)	0.004	.
0.94 (0.85-1.04)	0.248	.	1.20 (1.08-1.33)	<.001	.	1.10 (1.01-1.19)	0.030	.
1.51 (1.33-1.72)	<.001	<.001	1.04 (0.91-1.18)	0.564	0.001	0.81 (0.73-0.90)	<.001	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.68 (1.48-1.91)	<.001	.	1.23 (1.09-1.40)	0.001	.	0.99 (0.90-1.09)	0.865	.
0.97 (0.84-1.13)	0.716	0.936	1.83 (1.53-2.18)	<.001	<.001	1.39 (1.18-1.64)	<.001	<.001
0.99 (0.87-1.12)	0.862	.	1.52 (1.31-1.77)	<.001	.	1.44 (1.29-1.61)	<.001	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	.	.		.	.		.	.
	.	.		.	.		.	.
	.	.		.	.		.	.
	.	.	1.89 (1.45-2.46)	<.001	.	2.43 (2.03-2.91)	<.001	.
	.	.	1.74 (1.48-2.05)	<.001	.	3.21 (2.89-3.55)	<.001	.
	.	.	1.22 (0.97-1.55)	0.094	.		.	.
	.	.	2.40 (2.00-2.89)	<.001	.		.	.
	.	.	1.01 (1.00-1.02)	0.066	.		.	.
	.	.	1.02 (0.99-1.04)	0.178	.		.	.
	.	.	1.02 (0.99-1.04)	0.171	.		.	.
	.	.		.	.	0.99 (0.98-1.00)	0.260	.
	.	.		.	.	1.01 (1.00-1.02)	0.012	.
	.	.		.	.	1.63 (1.43-1.86)	<.001	.
	.	.		.	.	1.32 (1.14-1.52)	<.001	.
	.	.		.	.	1.51 (1.33-1.71)	<.001	.
	.	.		.	.	1.35 (1.15-1.59)	<.001	.

Appendix Table 5.6: *Specific CDC-B and CDC-C (AIDS) events occurring in individuals on ART with undetectable viral load between 2000 and 2023.*

		All events		0-50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Aspergillosis, invasive pulmonary	13	0.4%	2	0.7%
	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis oropharyngeal	894	26.2%	82	29.5%
	Candidiasis vulvovaginal, frequent/persistent	56	1.6%	1	0.4%
	Cardiomyopathy, HIV-related	6	0.2%	0	0.0%
	Cardiomyopathy, with HIV-related component	27	0.8%	1	0.4%
	Diarrhea, HIV-related >=30 days	62	1.8%	1	0.4%
	Fever e.c.i. / HIV-related	6	0.2%	0	0.0%
	HIV-associated nephropathy (HIVAN)	22	0.6%	2	0.7%
	Herpes zoster, multidermatomal	35	1.0%	3	1.1%
	Herpes zoster, recurring / multidermatomal unspecified	197	5.8%	6	2.2%
	Herpes zoster, unidermatomal recurrent	49	1.4%	3	1.1%
	Listeriosis	1	0.0%	0	0.0%
	Myelopathy, HIV-related	10	0.3%	0	0.0%
	Neuropathy, HIV-related	120	3.5%	2	0.7%
	Neuropathy, with HIV-related component	114	3.3%	1	0.4%
	Nocardiosis	2	0.1%	1	0.4%
	Oral Hairy Leucoplakia (OHL)	55	1.6%	1	0.4%
	Pelvic inflammatory disease	9	0.3%	0	0.0%
	Thrombocytopenia, HIV-related	130	3.8%	4	1.4%
	Thrombocytopenia, with HIV-related component	39	1.1%	5	1.8%
	Weight loss >10%, HIV-related / unknown cause	35	1.0%	2	0.7%
Subtotal		**1883**	**55.2%**	**117**	**42.1%**

CD4 category										
	050–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
3	0.5%	1	0.1%	1	0.2%	2	0.3%	4	0.9%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
211	32.3%	175	25.4%	146	23.0%	160	22.5%	120	27.0%
5	0.8%	9	1.3%	17	2.7%	19	2.7%	5	1.1%
2	0.3%	0	0.0%	2	0.3%	1	0.1%	1	0.2%
4	0.6%	3	0.4%	4	0.6%	8	1.1%	7	1.6%
6	0.9%	16	2.3%	9	1.4%	22	3.1%	8	1.8%
1	0.2%	2	0.3%	0	0.0%	1	0.1%	2	0.5%
4	0.6%	3	0.4%	5	0.8%	5	0.7%	3	0.7%
1	0.2%	7	1.0%	6	0.9%	12	1.7%	6	1.4%
23	3.5%	52	7.6%	39	6.1%	47	6.6%	30	6.8%
6	0.9%	4	0.6%	4	0.6%	16	2.3%	16	3.6%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
4	0.6%	1	0.1%	1	0.2%	1	0.1%	3	0.7%
8	1.2%	15	2.2%	30	4.7%	40	5.6%	25	5.6%
9	1.4%	14	2.0%	32	5.0%	37	5.2%	21	4.7%
0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
13	2.0%	11	1.6%	10	1.6%	11	1.5%	9	2.0%
0	0.0%	4	0.6%	0	0.0%	3	0.4%	2	0.5%
25	3.8%	27	3.9%	31	4.9%	31	4.4%	12	2.7%
3	0.5%	12	1.7%	3	0.5%	14	2.0%	2	0.5%
5	0.8%	8	1.2%	6	0.9%	8	1.1%	6	1.4%
334	**51.1%**	**366**	**53.2%**	**346**	**54.4%**	**438**	**61.7%**	**282**	**63.5%**

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
CDC-C events	AIDS dementia complex – HIV encephalopathy	45	1.3%	5	1.8%
	Bacterial pneumonia, recurring	345	10.1%	14	5.0%
	CMV disease	19	0.6%	4	1.4%
	CMV esophagitis	2	0.1%	1	0.4%
	CMV meningo-encefalitis	1	0.0%	1	0.4%
	CMV pneumonitis	1	0.0%	0	0.0%
	CMV retinitis	19	0.6%	4	1.4%
	Candidiasis esophagitis	275	8.1%	29	10.4%
	Candidiasis lungs/bronchial/trachea	12	0.4%	2	0.7%
	Cervical cancer, invasive	14	0.4%	1	0.4%
	Coccidioimycosis, extrapulmonary / disseminated	1	0.0%	0	0.0%
	Cryptococcosis, extrapulmonary / disseminated	16	0.5%	5	1.8%
	Cryptosporidiosis	11	0.3%	4	1.4%
	Cystoisosporiasis	2	0.1%	0	0.0%
	HIV wasting	17	0.5%	7	2.5%
	HSV chronic ulcer	43	1.3%	2	0.7%
	HSV esophagitis	3	0.1%	0	0.0%
	HSV pneumonitis	2	0.1%	0	0.0%
	Herpes simplex virus	61	1.8%	7	2.5%
	Histoplasmosis, extrapulmonary / disseminated	4	0.1%	3	1.1%
	Kaposi sarcoma	125	3.7%	8	2.9%
	Leishmaniasis visceral	5	0.1%	1	0.4%
	Microsporidiosis	5	0.1%	2	0.7%
	Mycobacterium avium/kansasii, extrapulmonary / disseminated	27	0.8%	5	1.8%
	Mycobacterium avium/kansasii, pulmonary	5	0.1%	0	0.0%
	Mycobacterium other / unspecified, extrapulmonary / disseminated	10	0.3%	3	1.1%
	Mycobacterium other / unspecified, pulmonary	5	0.1%	0	0.0%
	Non-Hodgkin`s lymphoma (NHL)	192	5.6%	7	2.5%
	Pneumocystis jirovecii extrapulmonary	1	0.0%	0	0.0%
	Pneumocystis jirovecii pneumonia	73	2.1%	23	8.3%
	Primary CNS lymphoma	9	0.3%	1	0.4%
	Progressive multifocal leukoencephalopathy	22	0.6%	7	2.5%
	Toxoplasmosis of the brain	21	0.6%	8	2.9%
	Tuberculosis, extrapulmonary / disseminated	53	1.6%	4	1.4%
	Tuberculosis, pulmonary	80	2.3%	3	1.1%
Subtotal		**1526**	**44.8%**	**161**	**57.9%**
Total		**3409**	**100.0%**	**278**	**100.0%**

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

CD4 category										
	050–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
6	0.9%	8	1.2%	10	1.6%	7	1.0%	9	2.0%
54	8.3%	82	11.9%	86	13.5%	71	10.0%	38	8.6%
2	0.3%	3	0.4%	5	0.8%	2	0.3%	3	0.7%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
5	0.8%	2	0.3%	7	1.1%	1	0.1%	0	0.0%
65	10.0%	62	9.0%	44	6.9%	44	6.2%	31	7.0%
2	0.3%	4	0.6%	1	0.2%	2	0.3%	1	0.2%
4	0.6%	1	0.1%	2	0.3%	5	0.7%	1	0.2%
0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
7	1.1%	3	0.4%	0	0.0%	1	0.1%	0	0.0%
0	0.0%	1	0.1%	3	0.5%	2	0.3%	1	0.2%
1	0.2%	1	0.1%	0	0.0%	0	0.0%	0	0.0%
6	0.9%	1	0.1%	2	0.3%	1	0.1%	0	0.0%
7	1.1%	4	0.6%	5	0.8%	16	2.3%	9	2.0%
1	0.2%	0	0.0%	1	0.2%	0	0.0%	1	0.2%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	0.5%
6	0.9%	13	1.9%	16	2.5%	14	2.0%	5	1.1%
0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%
12	1.8%	27	3.9%	30	4.7%	32	4.5%	16	3.6%
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	0.2%
12	1.8%	5	0.7%	3	0.5%	2	0.3%	0	0.0%
1	0.2%	1	0.1%	0	0.0%	1	0.1%	2	0.5%
3	0.5%	3	0.4%	0	0.0%	1	0.1%	0	0.0%
1	0.2%	0	0.0%	2	0.3%	1	0.1%	1	0.2%
48	7.4%	45	6.5%	42	6.6%	31	4.4%	19	4.3%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
24	3.7%	12	1.7%	6	0.9%	7	1.0%	1	0.2%
3	0.5%	3	0.4%	1	0.2%	1	0.1%	0	0.0%
8	1.2%	4	0.6%	2	0.3%	1	0.1%	0	0.0%
6	0.9%	5	0.7%	1	0.2%	1	0.1%	0	0.0%
13	2.0%	7	1.0%	6	0.9%	12	1.7%	11	2.5%
17	2.6%	24	3.5%	15	2.4%	14	2.0%	7	1.6%
319	**48.9%**	**322**	**46.8%**	**290**	**45.6%**	**272**	**38.3%**	**162**	**36.5%**
653	**100.0%**	**688**	**100.0%**	**636**	**100.0%**	**710**	**100.0%**	**444**	**100.0%**