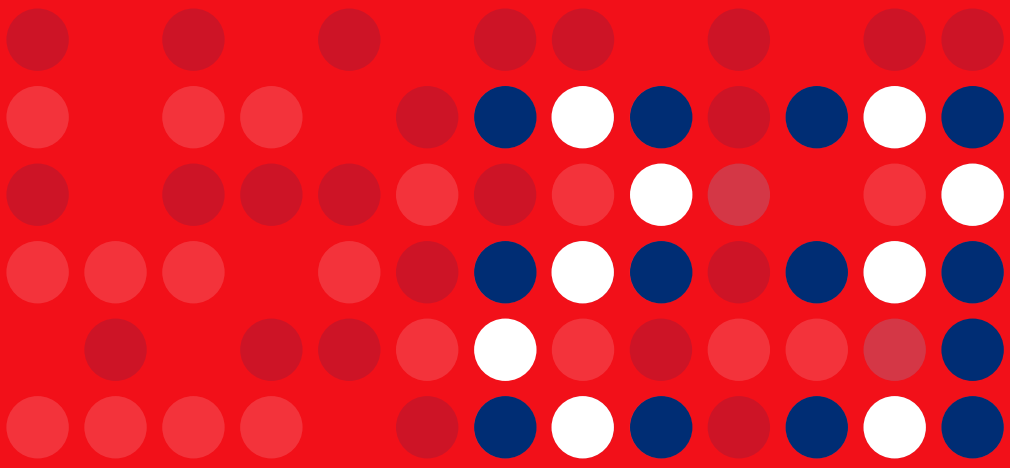
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2023

Chapter 3: Morbidity and mortality



3. Morbidity and mortality

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Introduction

Since the introduction of combined antiretroviral therapy (ART) in 1996, the life expectancy of people with HIV (PWH) has markedly improved[1]; in a subgroup of recently-diagnosed, effectively-treated individuals, it was shown to be similar to that of the general population in the Netherlands[2]. Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased[3], morbidity and/or mortality associated with non-AIDS-related diseases has increased among PWH during the ART era[4–9]. 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[13], bone disease, and non-traumatic bone fractures[13-15] have each been reported to be more common in PWH. Just as with individuals without HIV, traditional risk factors (such as tobacco use[17], alcohol abuse, and viral hepatitis co-infection[18]) 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[19,20].

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 30,132 adult individuals ever registered by SHM – that breaks down as 29,521 adults and an additional 611 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[21]. 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 2000-10, 2011-15, and 2016-22. We standardised these estimates according to the age distribution of the population during the period 2016-22 (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[22]. Indirect standardisation compares the incidence rates in the study and reference (period: 2016-2022) 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;
- smoking; and
- calendar period.

Mortality

Mortality was investigated in all 30,132 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 10.9 (9.6-12.4) (*Figure 3.1A*). Despite this 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 5.6 per 1,000 PYFU in 2022.

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 8.7 (7.3-10.2) per 1,000 PYFU in 2022.

Underlying causes of death

Observed underlying causes of death are presented in *Appendix Table 3.1*. Although the AIDS-related death rate has decreased significantly since the advent of 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[23]. *Table 3.1* shows the characteristics of adults with HIV who died of AIDS, compared to those who died of non-AIDS causes in the period 2013-2022. 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, with 61.2% qualifying as a very late presenter (CD4 cell count below 200 cells/mm^3). In addition, these individuals had much lower nadir CD4 cell counts. In 52.8% of cases, they did not have controlled viremia, and 18.1% 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 3.1*).

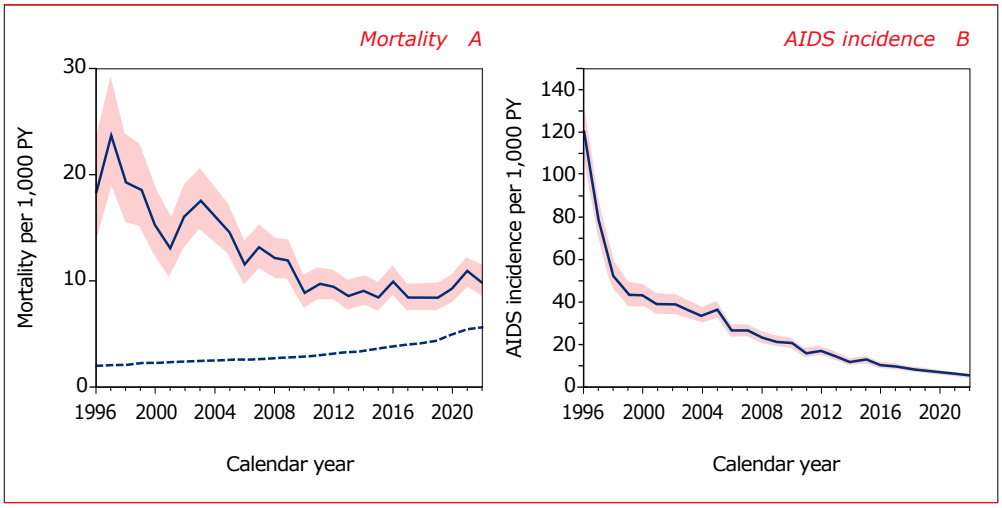
Among individuals who died of AIDS but did not classify as (very) late presenters (i.e. they had a CD4 cell count above 350 cells/mm^3 at diagnosis), the cause of death was relatively more likely to be an AIDS-related haematological malignancy, which are also known to occur in people on suppressive ART with high CD4 cell counts. The proportion and absolute number of deaths due to non-AIDS-defining conditions have increased significantly over time (*Figure 3.1.C*), primarily as a consequence of the ever increasing size and average age of the population of people with HIV in the Netherlands. People with HIV that were born in the Netherlands, MSM and men in general are overrepresented among those who died of non-AIDS causes, because people in these three (overlapping) categories have a higher average age compared to migrants, HIV transmission categories other than MSM, and women. Independent risk factors for death and for being diagnosed with an AIDS-defining condition are listed in *Appendix Table 3.2*.

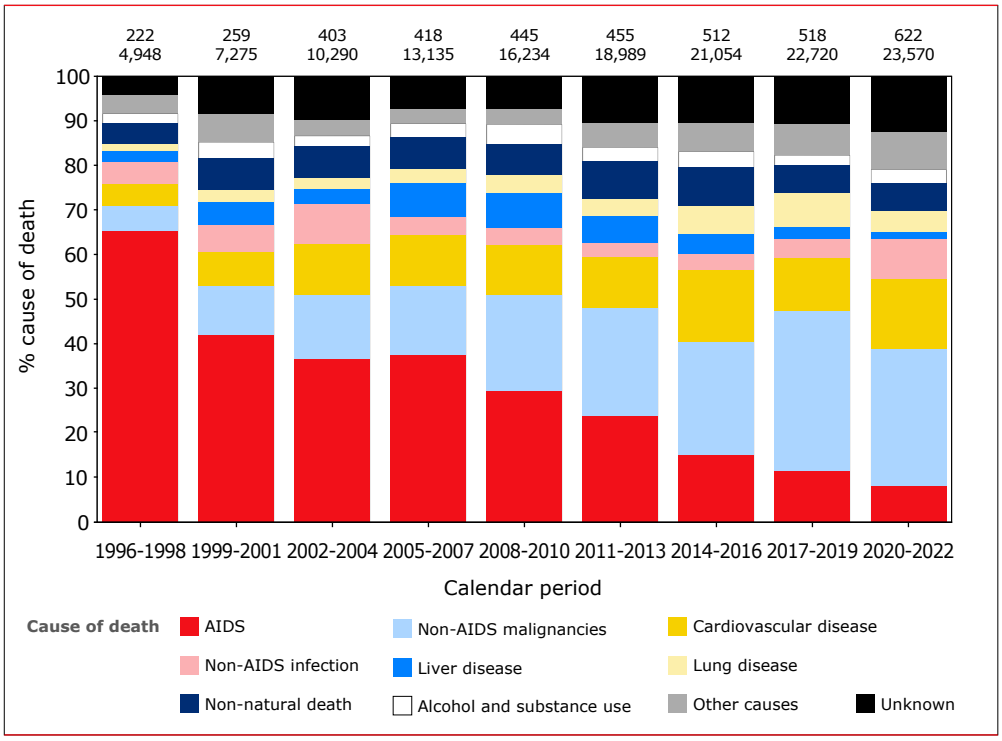
Table 3.1: *Characteristics of adults with HIV who died of AIDS compared to adults with HIV who died of non-AIDS causes in the period 2013-22.*

	Died of non-AIDS causes	Died of AIDS	p-value
Number of subjects	1561 (87.3%)	227 (12.7%)	
Age	60.1 (52.4-68.6)	55 (46-63.5)	<.001
Male gender	1355 (86.8%)	185 (81.5%)	0.039
Dutch origin	1113 (71.3%)	145 (63.9%)	0.024
MSM	892 (57.1%)	99 (43.6%)	<.001
Heterosexual transmission	417 (26.7%)	79 (34.8%)	0.014
Other transmission categories	252 (16.1%)	49 (21.6%)	0.046
Years since HIV diagnosis	15.6 (8.82-22.2)	7.95 (0.69-15.2)	<.001
Years since start cART	13 (6.8-18.4)	4.28 (0.34-12.4)	<.001
CD4 at HIV diagnosis	290 (110-510)	120 (40-322)	<.001
Late stage (CD4<350) at entry in care	878 (56.3%)	174 (77.3%)	<.001
Advanced stage (CD4<200) at entry in care	582 (37.3%)	139 (61.2%)	<.001
CD4 nadir	143 (50-260)	50 (17-130)	<.001
Last CD4 measured before death	500 (301-711)	150 (34-350)	<.001
Not undetectable at date of death	216 (13.9%)	115 (52.8%)	<.001
Not on cART at date of death	130 (8.3%)	41 (18.1%)	<.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/mm³.*

Figure 3.1.A-C: *(A) Annual mortality and (B) incidence of AIDS in 30,132 PWH in the Netherlands after entry into HIV care from 1996 onwards. Solid lines represent the incidence, while the shaded areas are the 95% confidence intervals. The dashed line is the mortality rate for age-matched and sex-matched individuals from the general population in the Netherlands. (C) 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.*





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 3.2*, including time-updated age and time-updated lagged CD4 cell counts, we found that, in general, risk of death was higher in men compared to women, and this risk increased as individuals grew older. It also increased if they:

- belonged to the HIV transmission risk group of people who use/used injecting drugs (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 people from sub-Saharan Africa, and other individuals not born in the Netherlands (with the exception of those born in Surinam or the Dutch Antilles), being lost to care (*Appendix Table 3.3*). In native Dutch individuals, and those from Surinam and the Dutch Antilles, 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 3.1*). The number of recorded suicides among people with HIV in the Netherlands in the period 2011 to 2022 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 10.5 instances per 100,000 individuals per year, compared to more than 40 instances per 100,000 person years in the population with HIV[24].

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 2022, a total of 165 instances of euthanasia were recorded; 30% of cases occurred in patients who died of AIDS, 39% in patients who died of non-AIDS-defining malignancies, and the remaining 31% 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 30,132 adult PWH ever registered in the SHM database, the incidence of first AIDS-defining events decreased sharply from 120.7 (95% CI 108.2-134.2) in 1996 to 5.2 (4.3-6.4) cases per 1,000 PYFU in 2022 (*Figure 3.1B*). *Appendix Table 3.4* gives an overview of the first AIDS-defining events occurring between 1996 and 2022. The most common first AIDS-defining events between 2016 and 2022 (n=1,168) were:

- *Pneumocystis jirovecii* pneumonia (22% of all events);
- oesophageal candidiasis (16%);
- Kaposi's sarcoma (10%);
- recurrent bacterial pneumonia (9%);
- tuberculosis (pulmonary 5%, extrapulmonary 3%);
- AIDS-defining lymphoma (7%);
- AIDS-related wasting (7%);
- cytomegalovirus-associated end organ disease (4%);
- toxoplasmosis of the brain (3%); and
- AIDS dementia complex/HIV encephalopathy (3%).

Risk factors for AIDS-defining events are shown in *Appendix Table 3.2*.

In the present analyses, we concentrate on the first occurrence of any AIDS-defining event after the start of 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 2022, 26,500 individuals contributed a total of 263.6 thousand PYFU, during which 3,185 CDC-B and/or CDC-C (AIDS-defining events) were diagnosed. This resulted in an incidence rate of 12.1 events per 1,000 PYFU (1,745 CDC-B events, 6.6 events/1,000 PYFU; 1,440 CDC-C/AIDS events, 5.5 events/1,000 PYFU) (*Table 3.2*). As expected, the incidence rates were highest in the CD4 strata below 200 cells/mm^3. Although the incidence rates declined sharply in the higher CD4 strata, the incidence rates in the 200-349 and 350-499 cells/mm^3 strata remained substantial, with 10.5 and 5.4 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 2.8 (95% CI 2.5-3.1) and 1.8 (1.6-2.2) events/1,000 PYFU, respectively. Note that the incidence in the over 750 cells/mm^3 stratum is statistically significantly lower than in the 500-749 cells/mm^3 stratum. In these highest CD4 strata, the main AIDS-defining events that still occurred were:

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

Appendix Table 3.6 shows the type and number of HIV-related diagnoses by CD4 strata).

Table 3.2: CDC-B and CDC-C/AIDS events occurring between 2000 and 2022 in individuals on ART, while having an undetectable viral load.

CD4 category (cells/mm³)	CDC events (n)	CDC B events (n)	CDC C events (n)	PYFU follow-up (x1000)	Incidence rate CDC events (/1000 PY) (95%CI)	Incidence rate CDC-B events (/1000 PY) (95%CI)	Incidence rate CDC-C events (/1000 PY) (95%CI)
0-50	259	102	157	0.6	446 (393-503)	175 (143-213)	270 (230-316)
50-199	610	316	294	8.9	68.4 (63.1-74.1)	35.5 (31.7-39.6)	33.0 (29.3-37.0)
200-349	647	342	305	29.1	22.3 (20.6-24.1)	11.8 (10.6-13.1)	10.5 (9.35-11.7)
350-499	597	319	278	51.5	11.6 (10.7-12.6)	6.19 (5.53-6.91)	5.40 (4.78-6.07)
500-749	659	401	258	92.8	7.10 (6.57-7.66)	4.32 (3.91-4.76)	2.78 (2.45-3.14)
750+	413	265	148	80.7	5.12 (4.63-5.63)	3.28 (2.90-3.70)	1.83 (1.55-2.15)
Total	**3185**	**1745**	**1440**	**263.6**	**12.1 (11.7-12.5)**	**6.62 (6.31-6.94)**	**5.46 (5.18-5.75)**

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 other mycobacterial infections

Between 1 January 1996 and 31 December 2022 a cumulative total of 1,152 cases of tuberculosis were diagnosed in 961 individuals, of which 674 (58.5%) were pulmonary cases and 478 (41.5%) were extrapulmonary/disseminated tuberculosis cases. During that same period, 549 cases of other mycobacterial infections were diagnosed in 485 individuals: 28 pulmonary and 311 extrapulmonary M. avium or M. kansasii cases, and 58 pulmonary and 152 extrapulmonary / disseminated cases of other atypical mycobacterial infections. *Figures 3.2.A & B* and *Appendix Table 3.4* describe the incidence over calendar time of tuberculosis and other mycobacterial infections.

Geographical region of origin

People who originated from sub-Saharan Africa (49.9%) or from south(-east) Asia (9.2%) were strongly overrepresented among the tuberculosis cases, while those who were born in the Netherlands (15.9%) and people from other western European countries (3.7%) were underrepresented. People originating from central and eastern European countries represented 3.6% and 2.4% of tuberculosis cases. Region of origin was not strongly associated with the incidence of the other (atypical) mycobacterial infections. *Table 3.3* describes some key characteristics of the individuals diagnosed with either tuberculosis or another mycobacterial infection. In case individuals had multiple diagnoses, the date of the first event was used.

Disease-related mortality rates

4.9% of the individuals diagnosed with pulmonary tuberculosis and 4.4% 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:

- 0% for pulmonary and 16.7% for extrapulmonary M. avium / kansasii infections;
- 6.9% for pulmonary and 20.4% for extrapulmonary other 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.

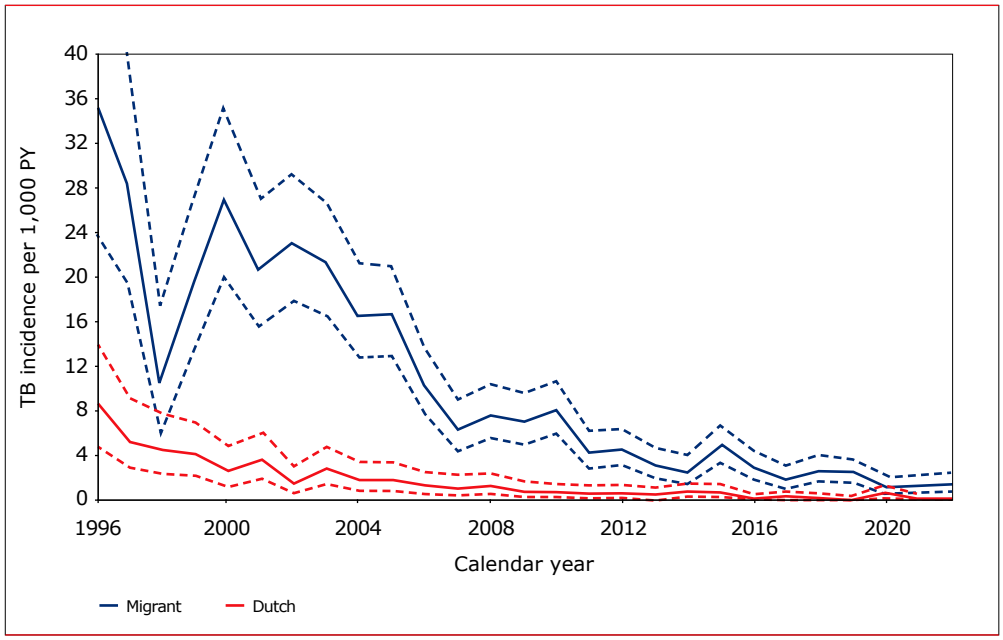
SHM has been collecting data on LTBI screening and treatment since 2018. IGRA testing during an episode in which active TB was diagnosed, was excluded from this dataset. A limitation of our analysis of LTBI screening is that we do not have data on whether, at the time of IGRA testing, the individual had complaints that may have been caused by tuberculosis, which then prompted the treating physician to perform IGRA testing. In 21.7% of cases an 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 1,906 individuals. In 184 (9.7%) of these individuals LTBI testing was positive, and 71 (38.6%) of those received a course of LTBI treatment. LTBI treatment consisted of:

- isoniazid plus rifampicin (typically for a duration of three months) in 22 individuals;
- isoniazid monotherapy (typically for a duration of six to nine months) in 39 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 184 individuals who tested positive on LTBI screening, 3 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, one case of pulmonary tuberculosis was diagnosed 3 years after diagnosis of untreated LTBI, and one case of pulmonary tuberculosis was diagnosed about 3 months after completion of a course of 9 months of isoniazid monotherapy. Of the 113 individuals with positive LTBI screening who did not receive LTBI treatment, 18 (15.9%) were known to have been diagnosed with and treated for active tuberculosis prior to the LTBI screening.

Figure 3.2.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).



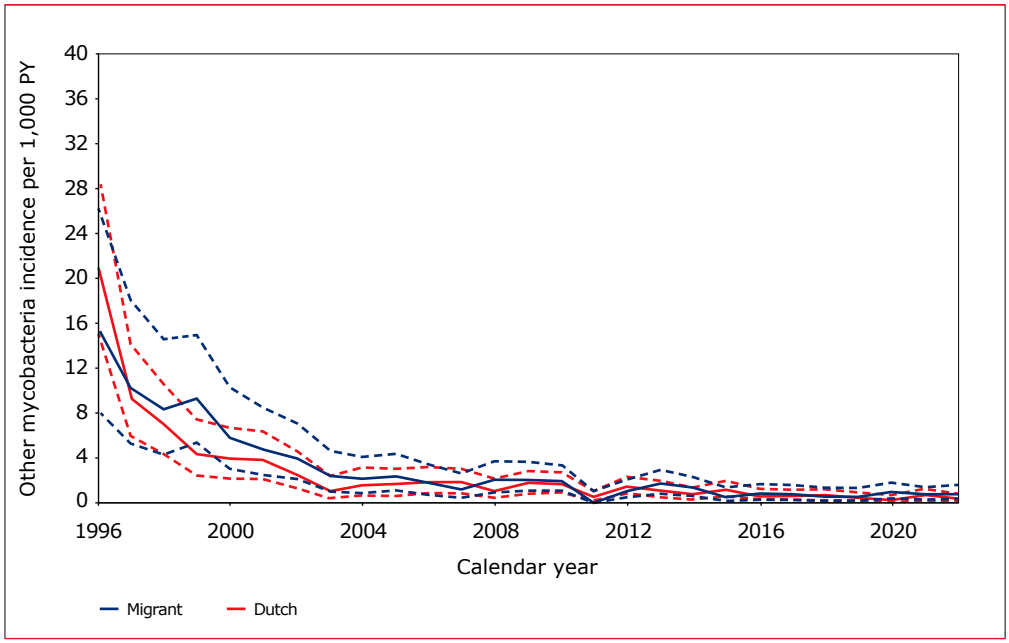


Table 3.3: Characteristics at the time individuals were diagnosed with tuberculosis or other mycobacterial infections for the first time.

	Tuberculosis	Other mycobacterial infections	p-value
Number of subjects	961 (66.5%)	485 (33.5%)	
Age	37 (30.7-44.6)	40.1 (34.6-47.8)	<.001
Male gender	638 (66.4%)	390 (80.4%)	<.001
Dutch origin	177 (18.4%)	275 (56.7%)	<.001
MSM	213 (22.2%)	219 (45.2%)	<.001
Heterosexuals	546 (56.8%)	186 (38.4%)	<.001
Other risk groups	202 (21.0%)	80 (16.5%)	0.042
Diagnosed before HIV diagnosis	222 (23.1%)	28 (5.8%)	<.001
Years since HIV diagnosis	0.91 (0.5- 4.5)	1.13 (0.59- 6.5)	0.004
Years since start cART	0.42 (0-1.09)	0.62 (0.25-1.24)	<.001
CD4 at HIV diagnosis	190 (60-400)	40 (10-190)	<.001
Late stage (CD4<350) at entry in care	439 (68.9%)	362 (85.0%)	<.001
Advanced stage (CD4<200) at entry in care	647 (67.3%)	380 (78.4%)	<.001
CD4 nadir	120 (40-243)	20 (10- 50)	<.001
Last CD4 measured before event	210 (100-367)	90 (25-180)	<.001
Not undetectable at date of event	792 (82.4%)	369 (76.1%)	0.005
Not on cART at date of event	690 (71.8%)	236 (48.7%)	<.001

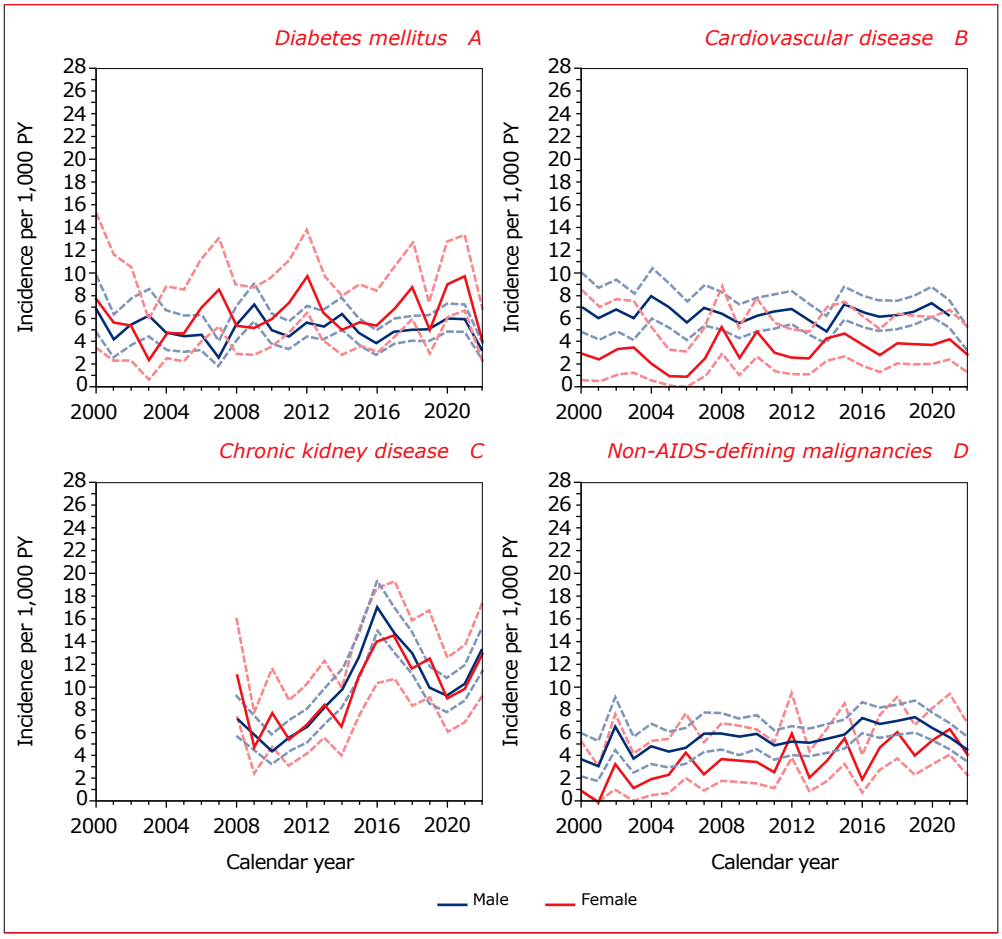
Non-AIDS-defining events

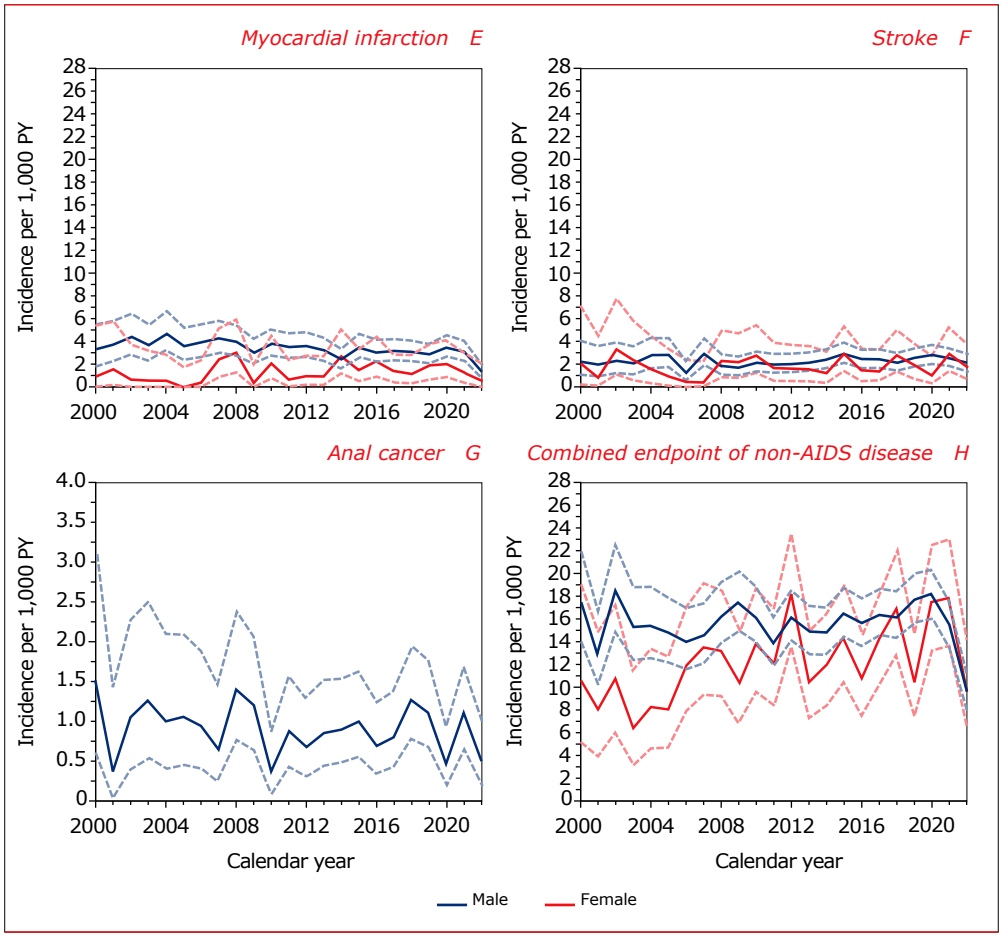
Of the 30,132 adult PWH ever registered with SHM, 29,786 were aged 18 years and over while in follow up in, or after January 2000. For these treated and untreated adults, we report incidence figures and risk factors for:

- 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 3.3.A-H*).

Figure 3.3.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 29,786 individuals aged 18 years and over, who were in follow up in, or after January 2000, a total of 1,751 (1,341 men and 410 women) were diagnosed with type 2 diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.3A*), and in 2022 was 3.1 (95% CI 2.3-4.2) per 1,000 PYFU in men and 4.0 (2.1-6.8) per 1,000 PYFU in women. In men, the age-standardised incidence ratio declined over time and was significantly lower in 2016-22 than in 2000-10 and 2011-15. In women, however, the age standardised incidence in 2000-10 and 2011-15 was not significantly different from that in 2016-22 (*Table 3.4*).

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

- male gender;
- non-Dutch origin (in particular people born in sub-Saharan Africa, south Asia, and the Caribbean);
- older age group;
- acquiring HIV heterosexually or through injecting drug use;
- a BMI greater than 25 kg/m^2 or below 18 kg/m^2;
- hypertension;
- a latest CD4 cell count below 200 cells/mm^3;
- pre-treatment with nucleoside analogue reverse transcriptase inhibitors (NRTIs) prior to starting ART;
- treatment with the integrase inhibitors bictegravir, dolutegravir or raltegravir (but not elvitegravir) and
- a prior AIDS diagnosis (*Appendix Table 3.5*).

Moreover, the risk of new-onset diabetes in the periods 2000-2010 and 2011-2015 was significantly higher than in the period 2016-2022. Starting ART within 12 months of the last negative HIV test was also associated with a lower risk of new-onset diabetes.

Table 3.4: *Crude incidence of diabetes mellitus per 1,000 person years of follow up in 2000–2010, 2011–2015 and 2016–2022 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)
2000–2010	5.2 (4.7–5.7)	1.41 (1.27–1.54)	5.8 (4.8–6.8)	0.92 (0.76–1.08)
2011–2015	5.3 (4.7–5.9)	1.22 (1.09–1.35)	6.8 (5.6–8.2)	1.02 (0.83–1.22)
2016–2022	4.9 (4.5–5.4)	1 (reference)	7.1 (6.1–8.2)	1 (reference)

**Standardised according to the observed age distribution between 2016–2021.*

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

Cardiovascular disease

From January 2000 onwards, 1,879 individuals (1,667 men and 212 women) had a fatal or non-fatal cardiovascular event. Of these:

- 922 had a myocardial infarction;
- 692 had a stroke;
- 138 had a coronary artery bypass graft;
- 675 had a coronary angioplasty or stenting; and
- 15 had a carotid endarterectomy.

The crude incidence over time remained stable and was lower in women than in men (*Figure 3.3B*). The age-standardised incidence ratio in men and women declined over time (*Table 3.5*).

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

- male gender;
- Dutch origin;
- older age group;
- acquiring HIV through MSM contacts or through injecting drug use;
- a latest CD4 cell count below 350 cells/mm^3;
- a prior AIDS diagnosis;
- pre-treatment with NRTIs before starting ART;
- use of abacavir (either currently or in the last six months);
- current use of dolutegravir or raltegravir (but not elvitegravir or bictegravir);
- current and past smoking;
- a BMI > 30 (obesity); and
- the presence of hypertension.

Estimated cardiovascular risk using the D:A:D algorithm was also higher during 2000-2010 and 2011-2015 than during 2016-2022, independent of other variables included in the analysis (*Appendix Table 3.5*). The strong positive association between use of abacavir and CVD was independent of renal function. When eGFR, estimated using the Cockcroft-Gault method (available from 2007 onwards), was included in the model the abacavir effect was only slightly attenuated, decreasing from an incidence risk ratio (IRR) of 1.60 to 1.48, $p<0.001$. 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 1.07 (95% CI 0.94-1.21);
- at 30-60 ml/min the IRR was 1.57 (1.31-1.89);
- at 15-30 ml/min, the IRR was 4.60 (3.27-6.49); and
- at 0-15 ml/min the IRR was 3.71 (2.20-6.24).

From January 2000 onwards, 252 men and 28 women experienced a fatal or non-fatal secondary cardiovascular event (156 had a myocardial infarction, 135 had a stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2022 in men and women with a prior cardiovascular event was 26.4 (23.3-29.9) and 21.5 (14.3-31.0), respectively. The crude rate and age-standardised incidence ratio (SIR; indirect method) of secondary myocardial infarction and stroke per 1,000 PYFU did not change significantly during 2000-2010 (crude rate: 29.7 events per 1,000 PYFU; SIR: 1.22, 95% CI 0.96-1.49), and 2011-2015 (crude rate: 23.7 events per 1,000 PYFU; SIR: 0.96, 95% CI 0.72-1.20) compared with the reference period 2016-2022 (crude rate: 25.0 events per 1,000 PYFU).

Table 3.5: *Crude incidence of cardiovascular disease per 1,000 person years of follow up in 2000–2010, 2011–2015, and 2016–2022 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)
2000–2010	6.5 (6.0–7.1)	1.60 (1.46–1.73)	2.9 (2.2–3.7)	1.40 (1.06–1.74)
2011–2015	6.3 (5.7–7.0)	1.23 (1.11–1.35)	3.4 (2.6–4.4)	1.19 (0.87–1.50)
2016–2022	6.3 (5.8–6.8)	1 (reference)	3.6 (2.9–4.4)	1 (reference)

**Standardised according to the observed age distribution in 2016–2022.*

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

Trends in cardiovascular risk factors

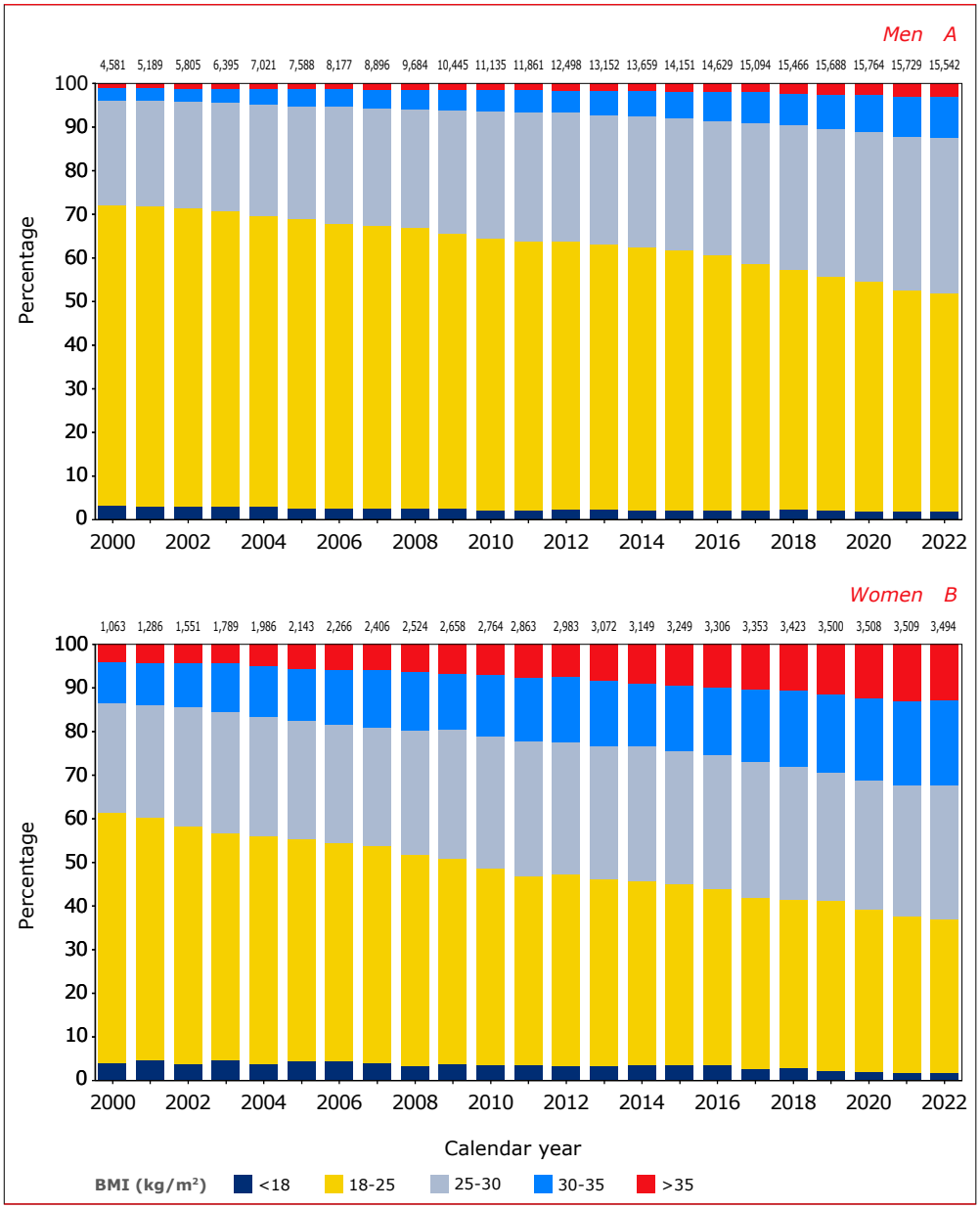
Figures 3.4A and *3.4B* show that the distribution of body mass index (BMI) of both men and women in the HIV-1-positive population has increased over time. In 2022, the proportion of men with available BMI data who were overweight (25-30 kg/m^2) or obese (WHO class I: 30-35 kg/m^2 and WHO class II/III: 35 kg/m^2 or over), was 36.1%, 9.6% and 2.4%, respectively. In women, these proportions were 30.9%, 19.6% and 12.4%, respectively.

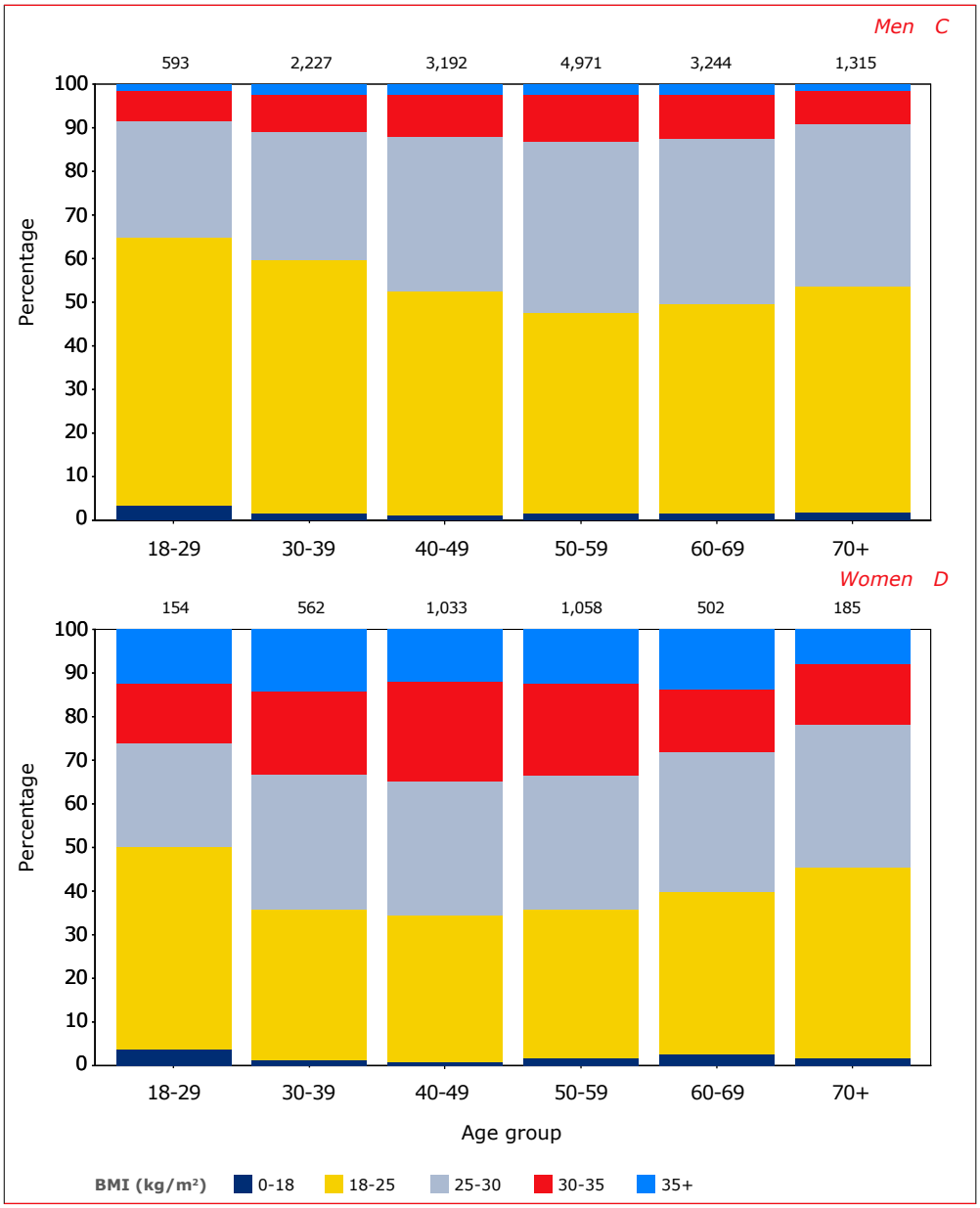
Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the population with HIV. This analysis revealed that the increase was at least partially driven by changes over time in population demographic characteristics (age, region of origin, HIV transmission category) and time since first 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. A recent paper using data from the ATHENA cohort, demonstrated that rapid weight gain on these agents is not readily reversible after switching to alternative regimens[25].

Figures 3.4C and *3.4D* show the distribution of BMI according to age groups in 2022 for men and women. Whereas in adult men of all age groups, the proportion classified as obese (12.0%) was somewhat lower than the proportion found in the general Dutch male population (14.1%), in women of all age groups there was more obesity (32.0%) than in the general Dutch female population (16.1%)[26]. There were substantial differences between those of Dutch origin, Western migrants and non-Western migrants: among males, 10.9% of Dutch men, 12.5% of Western migrants and 14.7% of non-Western migrants were obese. In females, however, those figures were 23.6%, 20.4%, and 38.3%, 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 2.28, 95% CI 2.01-2.60, p<0.001; obese IRR 5.53, 95% CI 4.79-6.39, p<0.001), but that was not the case with CVD, CKD or non-AIDS-defining malignancies (*Appendix Table 3.5*).

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 7 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.

Figure 3.4: *Distribution of the body mass index (BMI) at the end of each calendar year in (A) men, and (B) women, as a percentage of the total number of men and women with a known BMI in each year, and distribution of the BMI over the age groups for (C) men, and (D) women, in 2022. For each individual, the last available weight measurement in each year was selected. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year (A & B) or from that age group (C & D).*





Legend: BMI = body mass index.

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[27]. 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[27,28]. However, because the CKD-EPI equation is the one most often used in clinical practice, we have chosen to report eGFR values as estimated by this equation. The distribution of eGFR categories in ml/min/1.73m^2 (90 or above, normal kidney function; 60-89, mildly reduced; 30-59, moderately reduced; 15-29, severely reduced; and below 15, very severely reduced kidney function) is shown in *Figures 3.5A* and *3.5B* for men and women. The percentage of men with normal kidney function decreased over time from 74.5% in 2007, to 42.2% in 2022, and this pattern was similar in women. Typically, eGFR decreases with increased age, as shown in *Figure 3.6*, 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

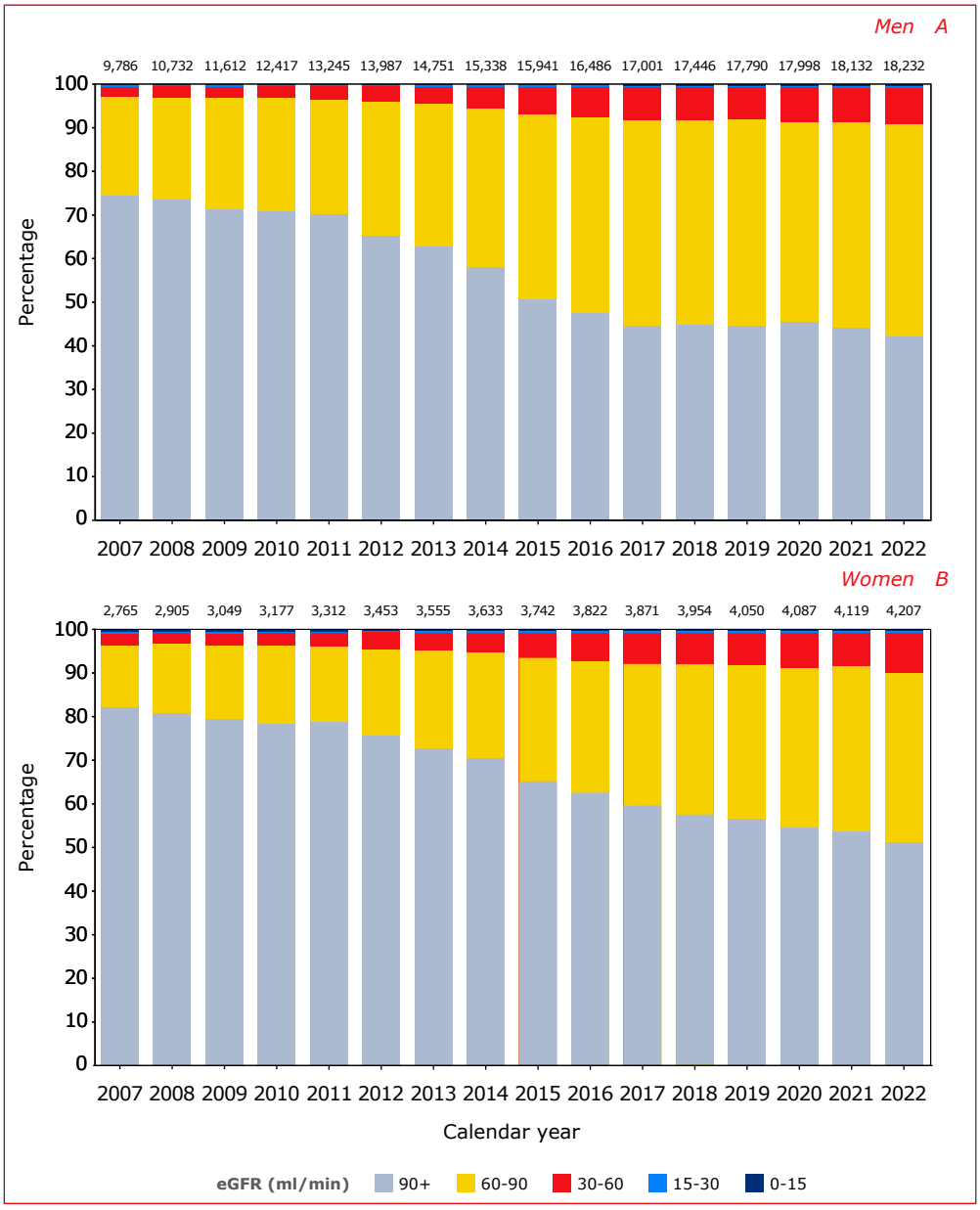
In individuals with an eGFR above 60ml/min/1.73m^2 at the time of inclusion in the analyses, who did not have a previously confirmed CKD, the crude incidence of CKD (defined as eGFR below 60ml/min/1.73m^2 confirmed by a second test at least 26 weeks later) varied over time (*Figure 3.3C*). Routine collection of serum creatinine measurements commenced in 2007. To avoid misclassifying prevalent CKD as incident CKD, we used serum creatinine levels measured in 2007 to distinguish between prevalent (i.e. CKD already present in 2007) versus new-onset incident cases of CKD (i.e. no CKD observed in 2007) from 2008 onwards. In men, the incidence rose from 7.1 cases per 1,000 PYFU in the period 2008-14 to 11.6 in 2015-22. In women, the incidence rose from 7.4 to 12.4 cases per 1,000 PYFU during the same periods (*Table 3.6*). The age-standardised incidence ratio in men and (to a lesser extent) women increased significantly over time (*Table 3.6*).

Risk factors for CKD included:

- female gender;
- Dutch origin;
- low current CD4 cell count (below 200 cells/mm^3);
- a prior AIDS diagnosis;
- belonging to the HIV transmission risk group of people who inject drugs;
- older age group;
- lower body mass index;
- hypertension;
- diabetes mellitus;
- cardiovascular disease;
- pre-treatment with monotherapy and dual therapy with nucleoside analogues before the start of ART; and
- chronic HBV and HCV co-infection (*Appendix Table 3.5*).

When current use of cobicistat, rilpivirine, dolutegravir, and bictegravir were added to the model, the increased risk of CKD in the calendar period 2016-2022 completely disappeared (even reversed) in comparison to 2008-2010 and 2011-2015. 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 3.5: *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.*

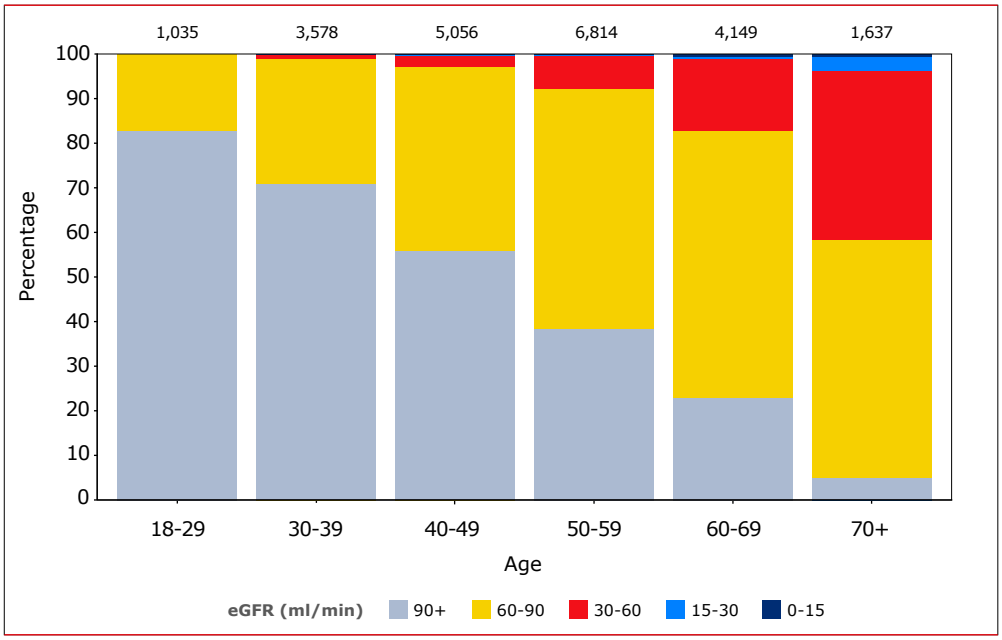
Table 3.6: Crude chronic kidney disease incidence per 1,000 person years of follow up in 2008-2014, and 2015-2022, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardized Inc. Ratio (95%CI)
2008-2014	7.0 (6.3-7.8)	0.81 (0.72-0.90)	7.3 (5.7-9.0)	0.91 (0.71-1.11)
2015-2022	11.4 (10.7-12.2)	1 (reference)	12.1 (10.6-13.8)	1 (reference)

**Standardised according to the observed age distribution in 2015-2022.*

***Legend:** CI = confidence interval; PYFU = person years.*

Figure 3.6: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2022 for different age categories. For each individual, the last available measurement in 2022 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 2022, 2,293 diagnoses of non-AIDS-defining malignancies in 2,106 unique individuals were recorded in SHM's database. An additional 921 patients were diagnosed with one or more non-melanoma skin cancers, but these were not included in the present analysis. *Table 3.7* shows the most common types of non-AIDS-defining cancer:

- lung cancer (16.2%);
- intestinal cancer (mainly oesophageal, gastric, intestinal, and rectal cancers, but excluding hepato-cellular carcinoma, 13.5%);
- haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 13.4%);
- invasive anal cancer (excluding pre-malignant AIN, 11.5%);
- prostate cancer (10.4%); and
- head and neck cancers (8.3%).

Figure 3.7 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 3.8*, 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 3.3D*. The age-standardised incidence in men was statistically significantly lower in the period 2016-2022, compared to 2000-2010, and borderline significantly lower compared to 2011-2015 (*Table 3.8*). 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 3.8*).

Demographic and clinical factors independently associated with an increased risk of a first non-AIDS-defining malignancy were (*Appendix Table 3.5*):

- older age group;
- acquiring HIV-1 through injecting drugs or contact with blood or blood products;
- lower current CD4 cell count (CD4 below 350 cells/mm^3);
- low body mass index;
- prior AIDS;
- chronic HBV co-infection; and
- current or past smoking.

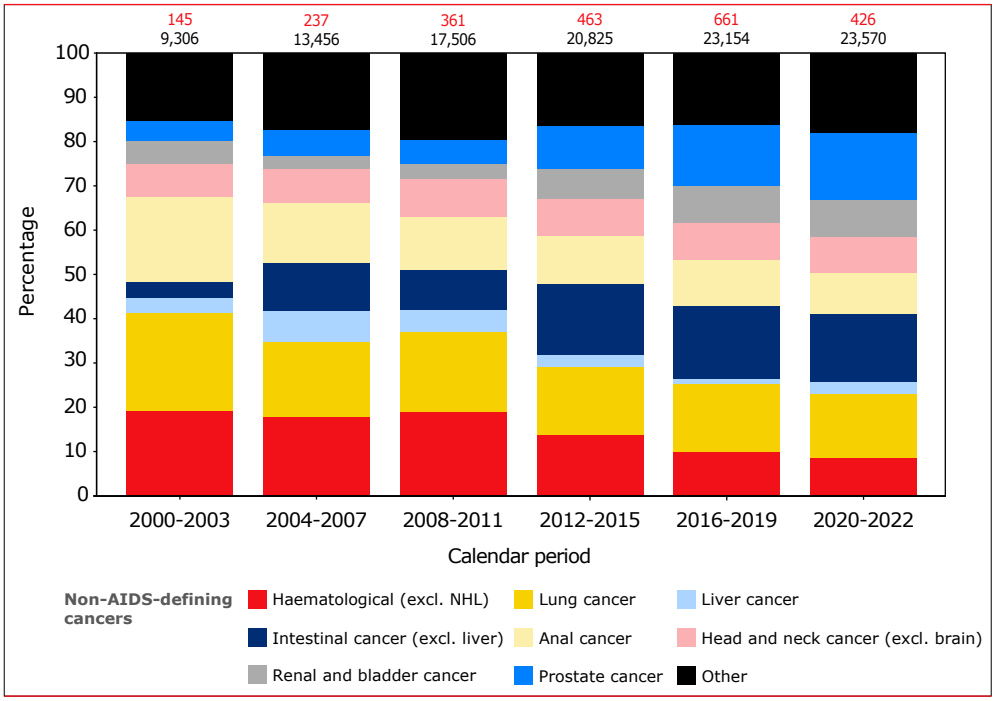
Furthermore, people who had been pre-treated with mono or dual-NRTI-based regimes prior to starting ART had an independently increased risk for NADM, compared with those who were therapy-naïve prior to starting ART (relative risk [RR] 1.17, 95% CI 1.01-1.34). Of note, independent of all other risk factors investigated, people who initiated ART within 12 months of their last negative HIV test had a significantly lower risk for NADM (RR 0.62, 95% CI 0.43-0.88) 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 2022, the overall five-year survival rate following the most common non-AIDS-defining malignancies are shown in *Table 3.7* and *Appendix Figure 3.1*. Table 3.7 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 18.9% in the period 2000-2022, to 50.7% in the period 2013-2022, however because of low numbers the uncertainty of this latter estimate is high. For nearly all other NADM we observed an improvement in the crude 5-year survival rates of a few percentage points (but with slightly better results for lung cancer and malignant melanoma).

Anal cancer

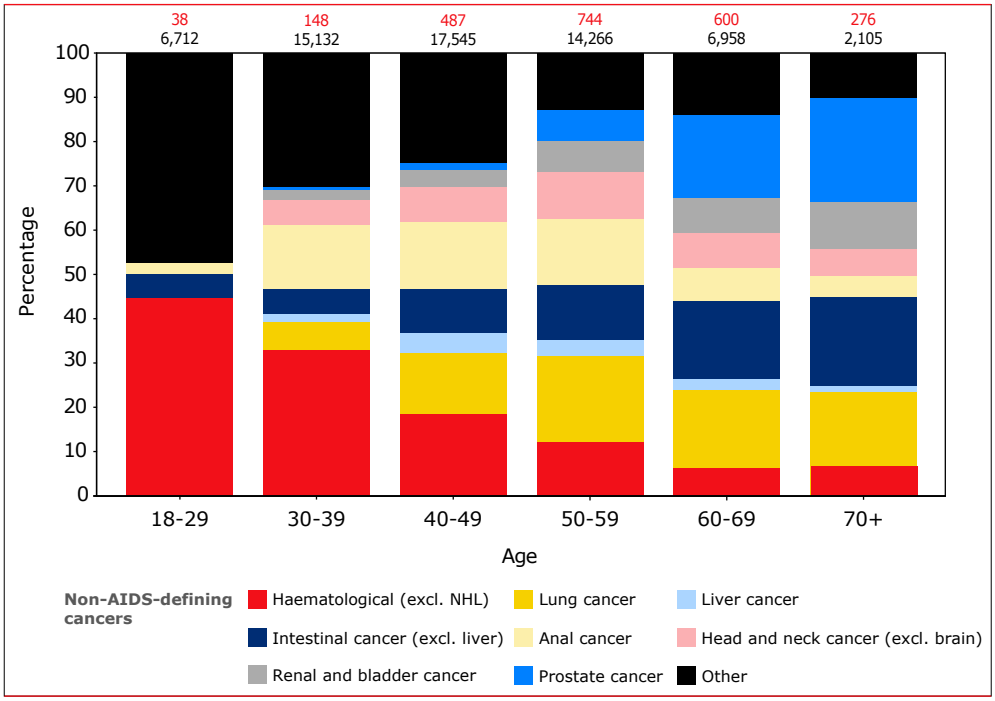
In total, 253 men with HIV and 11 women with HIV were diagnosed with anal cancer. Among men with HIV, the incidence of anal cancer fluctuated between 0.4 and 1.5 cases per 1,000 PYFU between 2000 and 2022 (*Figure 3.3G*). A 2023 study examined trends in incidence of and mortality after anal cancer diagnosis in people living with HIV, including the effect of AIN/anal cancer screening from 2007 onwards, in the Netherlands [29]. 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 3.7: Relative changes in non-AIDS-defining malignancies between 2000 and 2022 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 3.8: 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 2022.



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

Table 3.7: Most common non-AIDS-defining malignancies diagnosed in 2000-2022, and a sub-group diagnosed between 2013-2022, excluding non-melanoma skin cancer and pre-malignant lesions found by cervical and anal screening.

			2000-2022			2013-2022
non-AIDS malignancy	**# of malignancies**	**%**	**Five-year survival (%)**	**# of malignancies**	**%**	**Five-year survival (%)**
Lung cancer	372	16.2	15.4	218	15.2	20.7
Intestinal cancer (excl. liver)	310	13.5	30.0	228	15.9	32.0
Hematological (excl. NHL)	307	13.4	61.8	156	10.8	64.7
Anal cancer	264	11.5	66.0	151	10.5	69.3
Prostate cancer	239	10.4	80.0	190	13.2	82.4
Head and neck cancer (excl. brain)	190	8.3	56.8	118	8.2	61.8
Renal and bladder cancer	149	6.5	61.1	116	8.1	62.3
Other cancers	120	5.2	40.8	70	4.9	41.3
Malignant melanoma	104	4.5	75.8	61	4.2	84.6
Liver cancer	70	3.1	18.9	29	2.0	50.7
Breast cancer	65	2.8	78.3	38	2.6	73.6
Testicular cancer	41	1.8	86.4	21	1.5	85.2
Gynecological cancer (excl. cervical)	34	1.5	69.9	17	1.2	74.6
CNS cancer	28	1.2	59.9	25	1.7	54.7

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

Table 3.8: Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up in 2000-2010, 2011-2015, and 2016-2022, 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)
2000-2010	6.6 (6.0-7.1)	1.34 (1.23-1.45)	3.2 (2.5-4.0)	1.20 (0.93-1.47)
2011-2015	6.6 (6.1-7.3)	1.05 (0.96-1.15)	4.4 (3.5-5.6)	1.10 (0.85-1.35)
2016-2022	8.0 (7.5-8.6)	1 (reference)	5.3 (4.4-6.2)	1 (reference)

**Standardised according to the observed age distribution in 2016-2022.*

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

Multimorbidity

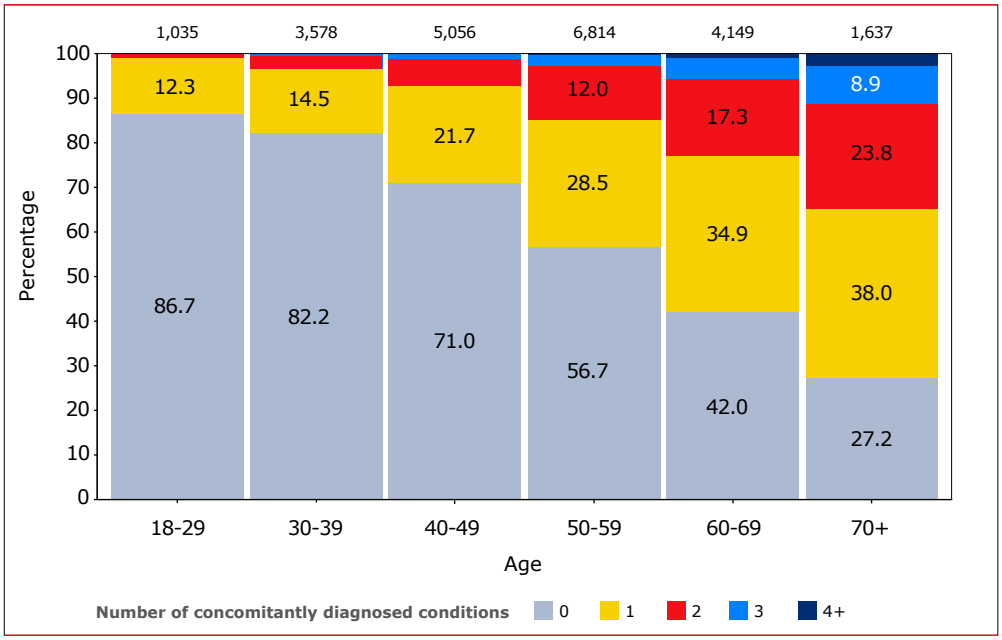
We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infections and AIDS diagnoses did not contribute to the multimorbidity count. The following comorbidities and conditions were taken into account:

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

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

Appendix Figure 3.2 shows the prevalence of each individual comorbidity over calendar time. *Figure 3.13* shows the distribution of the number of concomitantly-diagnosed conditions in various age categories of the adult population in 2022. The number of concomitant conditions was slightly higher in women than in men for all age categories (*Appendix Figure 3.3*). After adjusting for the variables listed in *Appendix Table 3.2*, multimorbidity was independently associated with increased risk of mortality (RR 2.11, 95% CI 2.04-2.19, p<0.001, per additional comorbidity diagnosed).

Figure 3.9: Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2022. 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 counted individual ATC codes (Anatomical Therapeutic Chemical classification system[a] of the comedications. Note that coformulated combinations, such as cotrimoxazole, have a single ATC code and therefore increase the comedication count by one.

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

In 2022, our count revealed:

- 18.4% of adults in active follow up had no recorded comedication use
- 29.4% used one comedication;
- 16.4% used two comedications;
- 10.9% used three comedications; and
- 7.2% used four comedications.

A further 18.4% 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 3.14*): 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 3.15A*) and those with more comorbidities (*Figure 3.16*) used more comedications. There were some differences between men and women, with women using slightly more comedications than men, while the most pronounced differences were to be found in the youngest age groups (*Figure 3.15B*). Finally, in adults receiving ART in the period 2007-2022, polypharmacy was also associated with an increased risk of death (RR 2.17, 95% CI 1.96-2.39, $p<0.001$) 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 2022 are listed in *Table 3.9*.

Table 3.9: Use of comedications in 2022.

Comedication use in 2022	N	%
ATC group	6710	12.1
Vitamins		
Lipid modifying agents	4714	8.5
Drugs for acid related disorders	3954	7.2
Agents acting on the renin-angiotensin system	3462	6.3
Psycholeptics drugs (antipsychotics, anxiolytics, hypnotics, sedatives)	3355	6.1
Antithrombotic agents	2875	5.2
Drugs for obstructive airway diseases	2732	4.9
Psychoanaleptics (antidepressants, psychostimulants)	2360	4.3
Drugs used in diabetes	2268	4.1
Mineral supplements	2120	3.8
Urological drugs	1808	3.3
Beta blocking agents	1673	3.0
Calcium channel blockers	1585	2.9
Antianemic drugs	1235	2.2
Antibacterial drugs	1183	2.1
Diuretic drugs	1182	2.1
Sex hormones and modulators of the genital system	1120	2.0
Corticosteroids systemic	1010	1.8
Topical dermatological corticosteroids	885	1.6
Analgesic drugs	870	1.6
Antiepileptic drugs	842	1.5
Cardiac therapy	750	1.4
Nasal preparations	727	1.3
Antiviral drugs	711	1.3
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	506	0.9
Antimycotic drugs	505	0.9
Drugs affecting bone structure and mineralization	453	0.8
Thyroid therapy	379	0.7
Ophthalmological drugs	309	0.6
Immunosuppressants drugs	282	0.5
Other nervous system drugs	259	0.5

Figure 3.10: 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.

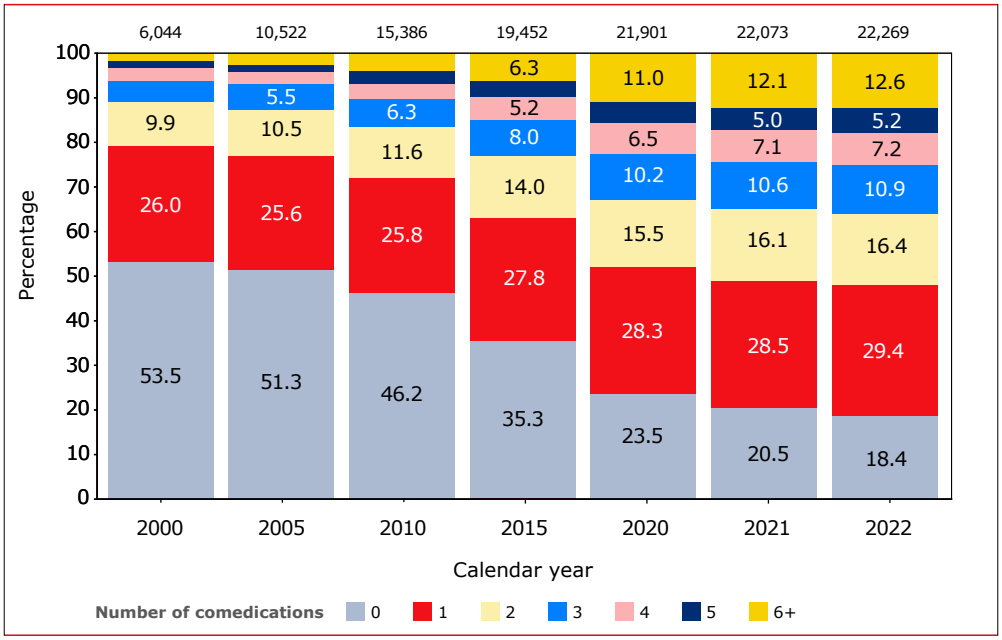
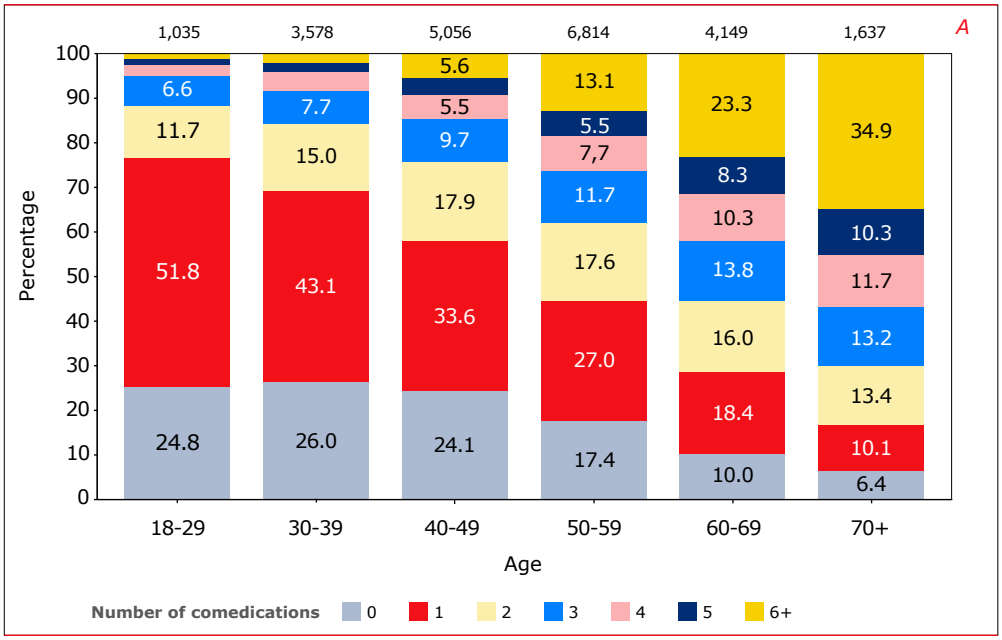


Figure 3.11: Number of comedications used by (A) age group, and (B) gender in 2022. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



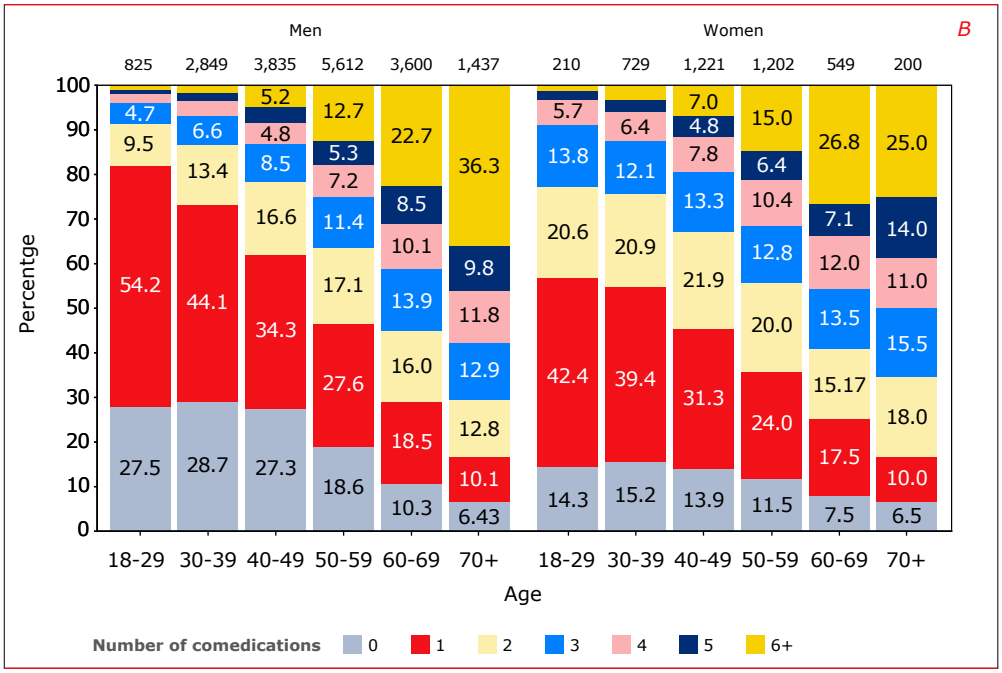
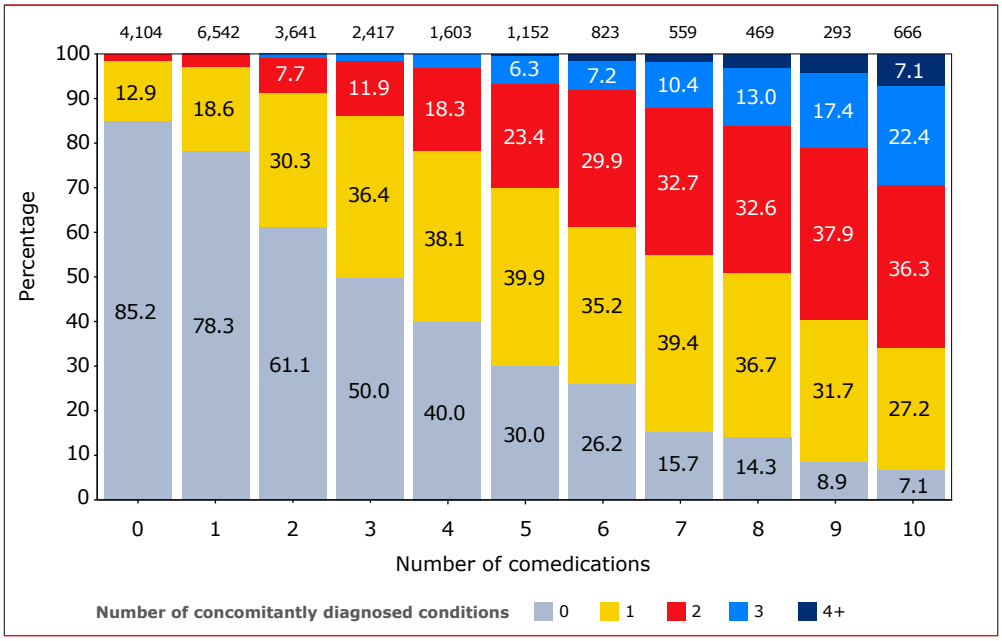


Figure 3.12: Number of comedications used in relation to the number of prevalent comorbidities. The numbers at the top of each bar represent the number of individuals contributing data to that category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per category.



SARS-CoV-2 and COVID-19

The first documented case of SARS-CoV-2 infection in the Netherlands was on 27 February 2020[30]. The majority of SARS-CoV-2 infections result in a self-limiting disease with minor or mild symptoms. In the Netherlands, the SARS-CoV-2 vaccination program started in January 2021. At the start of the SARS-CoV-2 vaccination program, PWH as a group were not prioritized, instead initially only the oldest PWH and those living in a nursing home were eligible. As of April 2021 all PWH became eligible for SARS-CoV-2 vaccination. National treatment guidelines for moderate and severe COVID-19 cases were continuously updated throughout the epidemic. These guidelines did not consider HIV status to be at strongly increased risk factor for severe COVID-19. Individuals however who are older, male, belong to non-Western ethnic groups, with lower socio-economic status, and those with certain underlying conditions like obesity, hypertension, renal dysfunction, diabetes mellitus, and cardiovascular disease, are at increased risk for severe COVID-19, hospitalization and death. Many of the risk factors for severe COVID-19 in the general population are more prevalent in people living with HIV. 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[31]. Here we present an updated analysis of the incidence, risk factors, and outcomes of COVID-19 in people living with HIV in the Netherlands using data collected up to 31 December 2022.

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. Details regarding diagnosis, disease severity, hospitalisations, and outcomes of COVID-19 are also collected. 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. Risk factors for severe COVID-19 (hospitalisation and death), were investigated using multivariable logistic regression including relevant demographics (age, sex, region of origin), general risk factors (comorbidities), and HIV-related parameters.

By the time of database closure for this analysis on 31 September 2023, SHM had collected data on 6,179 COVID-19 events diagnosed between 1 February 2020 and 31 December 2022 in 5,690 individuals (Figure 3.13.A). A total of 489 COVID-19 events occurred in individuals who had previously been diagnosed with COVID-19. Of the 6,147 recorded COVID-19 events, 243 (3.9%) resulted in hospitalisation (Figure 3.13.B); 39 (0.6%) of which required ICU admission. An additional 76 (1.2%) individuals presented with COVID-19 at an emergency room but required no hospitalisation, and the remaining 5,860 (94.8%) individuals remained at home. First COVID-19 events were slightly more likely to result in hospitalization (4.1%) compared to second COVID-19 events (2.0%). Table 3.10 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 is also described in *Table 3.10*. 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 3.10*).

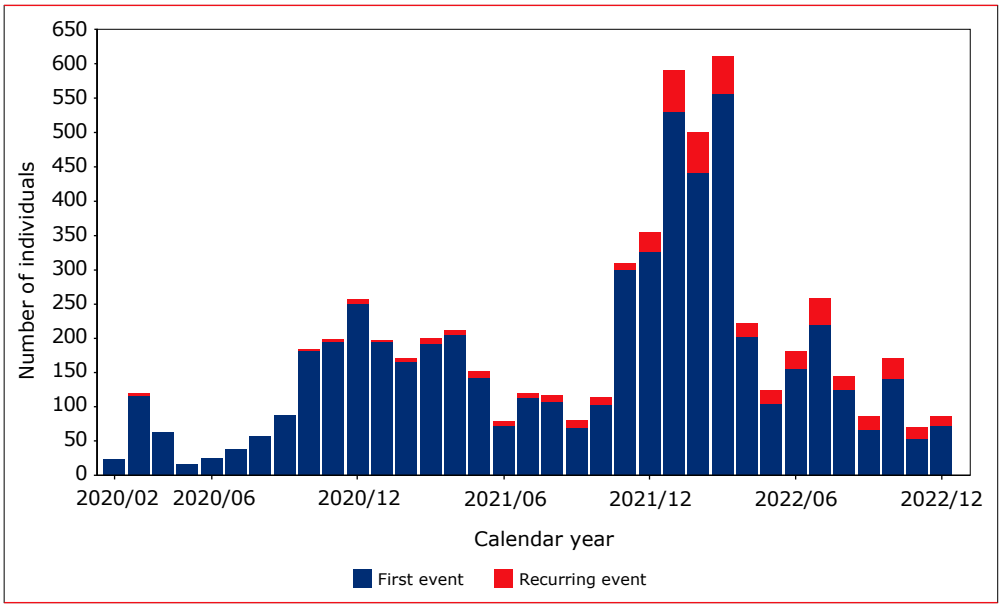
The bottom half of *Table 3.10* shows the distribution of selected comorbidities among individuals diagnosed with COVID-19. All investigated comorbidities were much more prevalent among the group that was hospitalised, resulting in a higher total multimorbidity count in the hospitalised group.

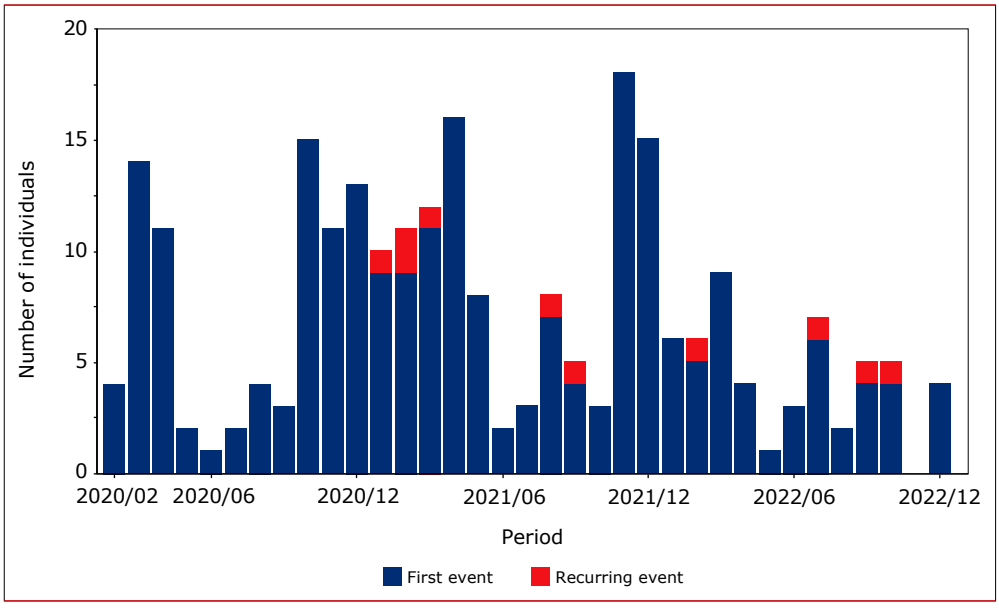
Multivariable logistic regression showed that independent risk factors for hospitalisation for COVID-19 among people living with HIV were higher age, migrant status (with higher risk in individuals originating from sub-Saharan Africa or, to a lesser extent, from Latin America), obesity (BMI over 30 kg/m^2), having a current CD4 count below 500 cells/mm^3 (the risk was even higher when the CD4 cell count was below 200 cells/mm^3), having a current viral load above 200 c/mL, and having had a prior AIDS-defining illness (*Table 3.11*). All other demographic, comorbidity, HIV-related and ART-related parameters investigated were not independently associated with a higher risk of being hospitalised following a diagnosis of COVID-19.

In total, 43 (0.76%) of the 5,690 individuals diagnosed with one (or more) COVID-19 event(s) were reported to have died as a direct result of COVID-19 (Figure 3.13.C). As is the case in the general population, the observed mortality rates increased strongly with increasing age (Figure 3.14.A) and in those diagnosed with co-morbidities (Figure 3.14.B). *Table 3.12* shows the demographics, HIV-related characteristics, and comorbidities of those who died from COVID-19, compared to those who survived. As expected, there were very substantial differences. Because of the low number of COVID-19-related deaths, statistical power to formally explore risk factors using regression analysis is low. Exploratory multivariable logistic regression models showed that independent risk factors for COVID-19-related mortality were higher age, having a sub-Saharan African or Latin American origin, having a higher number of concomitantly diagnosed comorbidities, and having a current CD4 count below 500/mm^3 (with the risk being even higher when the CD4 cell count was below 200/mm^3, Figure 3.14.C) (*Table 3.13*).

The SARS-CoV-2 Omicron strain has become the dominant circulating strain in the Netherlands since the end of December 2021. Comparing the pre-Omicron to the Omicron period, the hospitalization rate has decreased from 190 (6.04%) hospitalizations out of 3,146 COVID-19 events in the pre-Omicron period, down to 53 (1.75%) out of 3,033 COVID-19 events in the Omicron era. The COVID-19-related death rate has decreased from 34 (1.08%) out of 3,146 COVID-19 events in the pre-Omicron period, down to 9 (0.30%) out of 3,033 COVID-19 events in the Omicron period. Limiting the multivariable regression analyses of risk factors for COVID-19-related hospitalizations and deaths to the Omicron period, resulted in very similar findings indicating that the identified risk factors for severe COVID-19 outcomes have not changed since the Omicron period began, with older age and more comorbidities remaining to have the strongest associations with risk for hospitalization and death (data not shown).

Figure 3.13.A-C: Incidence of COVID-19 diagnoses (A), hospitalizations (B) and deaths (C) over calendar time.





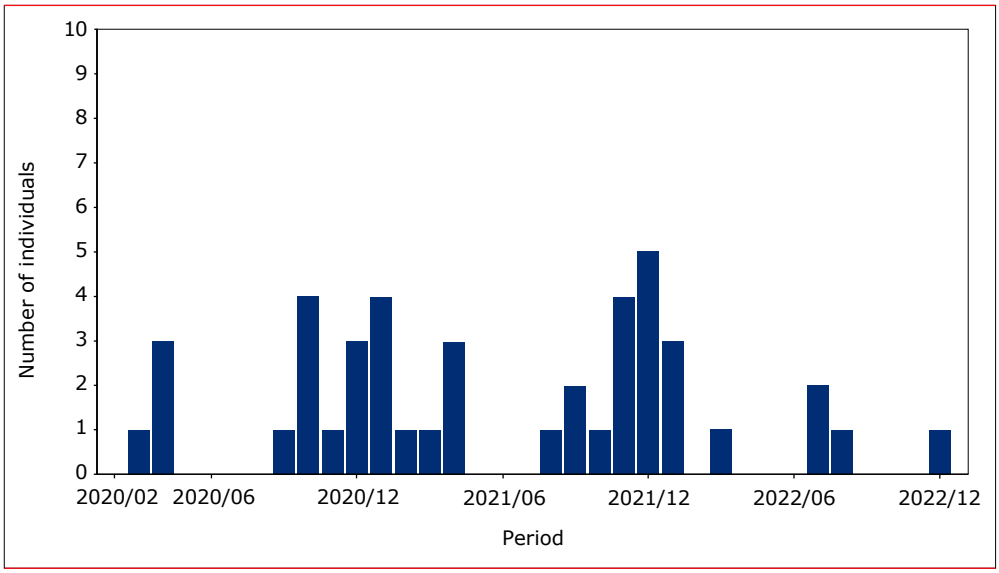
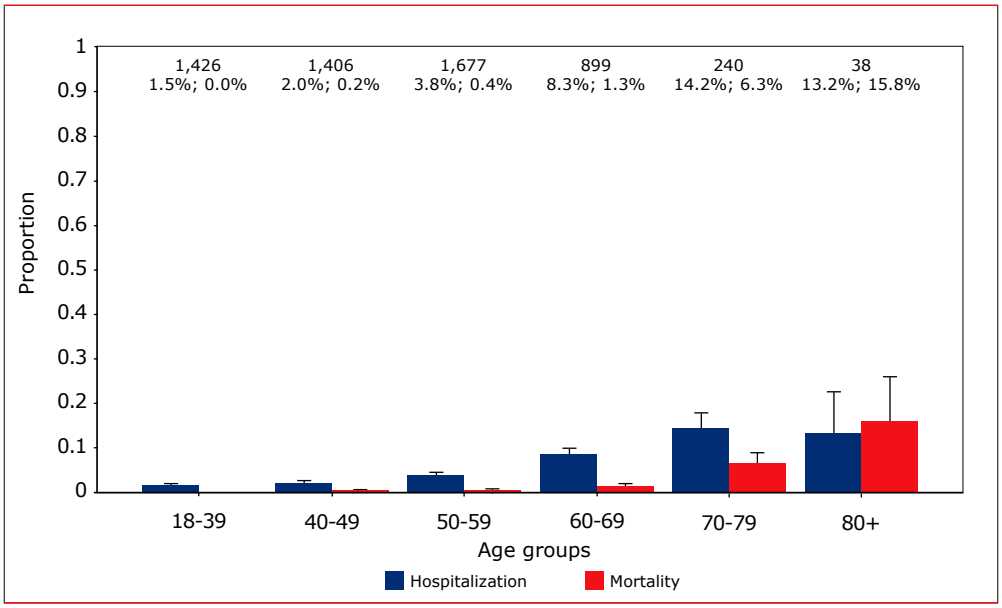
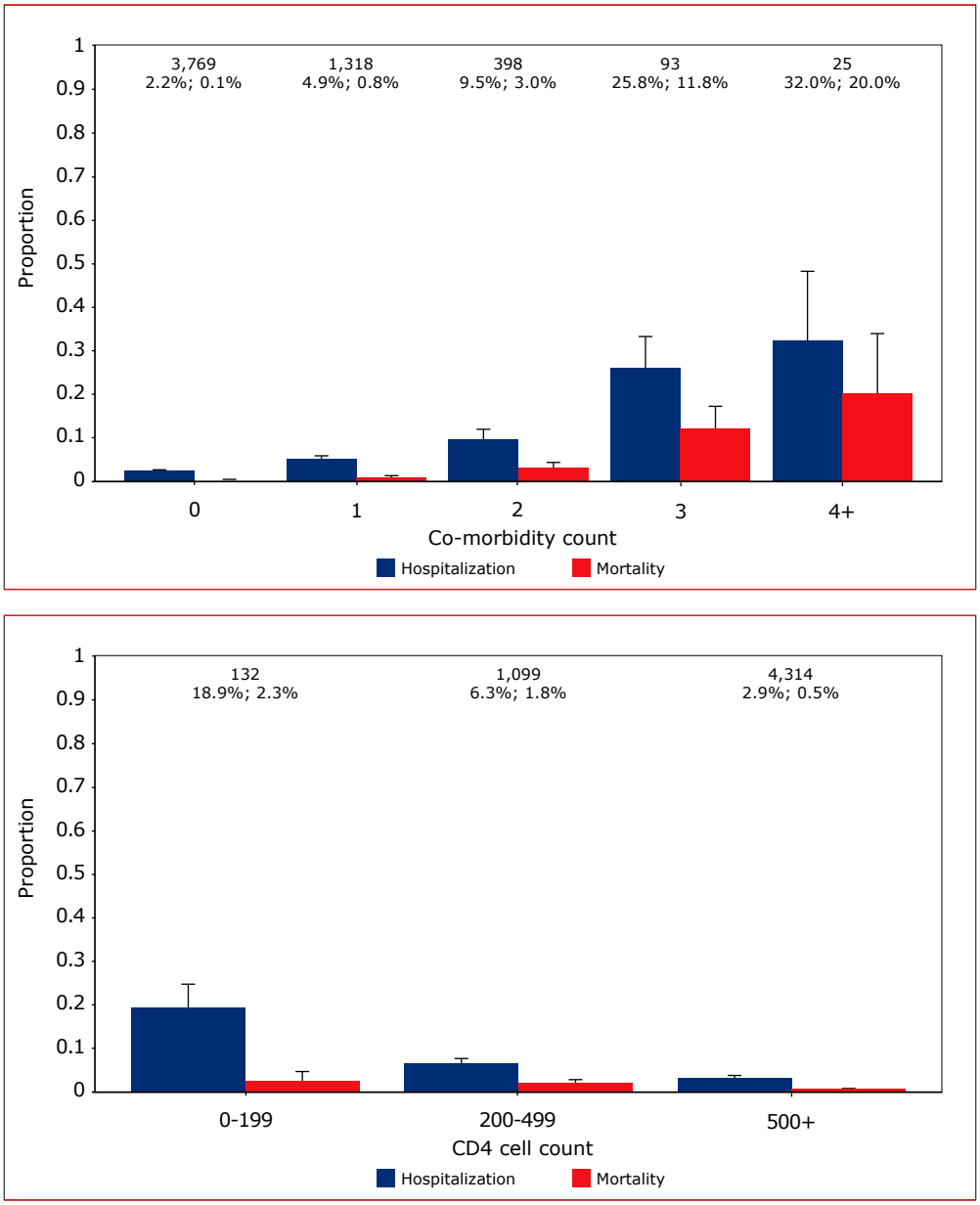


Figure 3.14.A-C: Proportions of COVID-19-related hospitalization and mortality by age group (A), co-morbidity count (B), and CD4 cell count category (C).





Legend: *The numbers at the top of the panels denote the number of individuals (top row) and the percentage of hospitalized and deceased individuals (bottom row) in each category.*

Table 3.10: Characteristics of individuals diagnosed with COVID-19.

	All PWH in 2022	Hospitalised	Not hospitalised
N	**21,901**	**233**	**5457**
Age, years	51.1 (41.3-59.0)	59.8 (51.4-66.7)	49.5 (39.4-57.9)
Male sex	81.8%	80.3%	81.6%
HIV transmission category			
MSM	63.5%	44.6%	66.2%
Other men	18.3%	35.6%	15.4%
Women	18.2%	19.7%	18.4%
Region of origin			
Netherlands / Europe / North America	69.8%	54.1%	63.9%
Sub-Saharan Africa	12.1%	16.7%	9.2%
Latin America / Caribbean	12.9%	18.0%	13.3%
Other regions	5.3%	11.1%	13.6%
Years known to be HIV positive	12.5 (7.2-18.6)	15.5 (8.8-22.0)	12.2 (6.6-18.4)
On ART	97.3%	96.9%	98.9%
HIV viral load >200 cps/mL	3.3%	8.4%	2.3%
Current CD4 count, mm^3	690 (507-905)	560 (360-790)	713 (530-920)
Nadir CD4 count, mm^3	250 (120-385)	160 (50-270)	263 (140-410)
Prior AIDS diagnosis	22.3%	40.3%	18.7%
Comorbidities			
Obesity (BMI>30 kg/m^2)	12.4%	26.8%	13.7%
Diabetes mellitus type 2	5.2%	20.5%	5.0%
Cardiovascular disease	3.6%	9.8%	3.3%
Stroke	1.8%	7.1%	1.8%
Hypertension (grade 2+ or on medication)	13.4%	30.4%	13.8%
Non-AIDS-defining malignancy	3.5%	9.8%	3.4%
Chronic kidney disease (eGFR<60 ml/min)	0.8%	6.3%	0.9%
Multimorbidity count			
0	62.2%	38.4%	68.5%
1	24.5%	30.4%	23.2%
2	9.9%	17.4%	6.7%
3 or more	3.4%	13.8%	1.6%

***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.*

Table 3.11: Predictors of hospitalisation among people living with HIV who were diagnosed with COVID-19.

	Univariable analysis		Multivariable model	
Risk factor	**Odds ratio (95%CI)**	**P-value**	**Odds ratio (95%CI)**	**P-value**
Male sex	0.81 (0.61-1.18)	0.35		
Age (per 10 years increase)	1.79 (1.60-2.01)	<0.0001	1.59 (1.39-1.81)	<0.0001
Region of birth				
Western	-ref-			
Sub-Saharan Africa	2.36 (1.63-3.43)	<0.0001	2.52 (1.67-3.80)	<0.0001
Latin America / Caribbean	1.45 (1.00-2.11)	0.053	1.54 (1.023-2.32)	0.039
Other	0.96 (0.62-1.49)	0.87	1.14 (0.72-1.79)	0.58
Number diagnosed comorbidities (per 1 more)	2.25 (1.98-2.55)	<0.0001	1.73 (1.50-1.99)	<0.0001
Current CD4 cell count (cells/mm^3)				
0 – 199	7.72 (4.78-12.46)	<0.0001	4.95 (2.88-8.49)	<0.0001
200 – 499	2.25 (1.67-3.03)	<0.0001	1.75 (1.28-2.38)	0.0005
500+	-ref-			
Nadir CD4 cell count (cells/mm^3)				
0 – 199	6.00 (3.14-11.48)	<0.0001		
200 – 499	2.90 (1.50-5.62)	0.0015		
500+	-ref-			
HIV viral load >200 copies/mL	2.03 (1.38-2.99)	0.0004	1.52 (0.99-2.34)	0.054
Prior AIDS diagnosis	2.90 (2.20-3.82)	<0.0001	1.77 (1.32-2.38)	0.0001

Table 3.12: Characteristics of individuals diagnosed with COVID-19 who died from COVID-19 compared to those who survived.

	Survived	Died of COVID-19
Number of individuals	5,647	43
Age, years	49.8 (39.6-58.2)	68.7 (60.6-78.1)
Male sex	81.5%	79.1%
HIV transmission category		
MSM	65.5%	44.2%
Other men	16.1%	34.9%
Women	18.5%	20.9%
Region of origin		
Netherlands / Europe / North America	63.5%	53.5%
Sub-Saharan Africa	9.5%	11.6%
Latin America / Caribbean	13.4%	30.3%
Years known HIV-positive	12.3 (6.6-18.5)	18.1 (12.8-24.0)
On ART	98.8%	95.4%
HIV viral load >200 cps/mL	2.5%	4.7%
Current CD4 cell count, cells/mm^3	710 (520-913)	443 (232-750)
Nadir CD4 cell count, cells/mm^3	260 (130-404)	90 (30-200)
Prior AIDS diagnosis	19.4%	37.2%
Comorbidities		
Obesity (BMI>30)	14.2%	20.9%
Diabetes mellitus	5.4%	30.2%
Cardiovascular disease	3.4%	20.9%
Stroke	1.8%	23.3%
Hypertension (grade 2+ or on medication)	14.1%	67.4%
Non-AIDS-defining malignancy	3.5%	18.6%
Chronic kidney disease (eGFR<60 ml/min)	0.9%	23.3%
Multimorbidity count		
0	67.7%	9.3%
1	23.5%	25.6%
2	6.9%	27.9%
3	1.5%	25.6%
4 or more	0.4%	11.6%

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.*

Table 3.13: Independent predictors of mortality among people living with HIV who were diagnosed with COVID-19.

Risk factor	Odds ratio (95%CI)	P-value
Age (per 10 years increase)	3.16 (2.27-4.41)	<0.0001
Region of birth		
Western	-ref-	
Sub-Saharan Africa	3.01 (1.01-8.97)	0.048
Latin America / Caribbean	3.49 (1.56-7.83)	0.0024
Other	0.61 (0.14-2.71)	0.51
Number of concomitantly diagnosed comorbidities (per 1 comorbidity increase)	2.43 (1.85-3.2)	<0.0001
Current CD4 cell count		
0-199	1.90 (0.40-9.09)	0.42
200-499	2.90 (1.47-5.70)	0.0021
500+	-ref-	

Summary and conclusions

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. The five-year survival rate after a first AIDS-defining condition is far greater than after a diagnosis of cardiovascular disease (CVD), or a non-AIDS-defining malignancy. Death is increasingly 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, although it is slowly approaching the latter. Furthermore, several studies have 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[32,33].

In 2021, for the first time there was a substantial increase in the mortality rate in people with HIV in the Netherlands during the period 2019 to 2021; from 8.48 deaths per 1000 person years in 2019, to 9.23 in 2020 and 10.91 in 2021. The increase in 2020 and 2021 appears mostly driven by an increase in the number of non-AIDS infectious causes of death, which include COVID-19-related deaths. 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 2021 (as well as in other Western countries). It is thought to be mostly driven by COVID-19-related deaths and other indirect adverse health effects of the COVID-19 epidemic in the Netherlands[34]. However, in 2022 the observed mortality rate of 9.79 deaths per 1000 person years has returned to pre-COVID-19 levels.

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. This decline may suggest improved awareness, prevention (including switching from drugs associated with an increased risk of diabetes mellitus[35] and myocardial infarction[36,37] (MI), 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[38]. 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[39].

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 0.63, 95% CI 0.42-0.94, p=0.023), independent of other traditional and HIV-related risk factors. The observation that the age-standardised incidence ratios for diabetes mellitus do not decline as much in women remains unexplained and needs further study – but the observed increasing average BMI and high (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[35,40,41]. Several of these risk factors are more prevalent among people with HIV[17].

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. 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[42]. 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[43]. 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 and CKD, but not cardiovascular disease and non-AIDS malignancies. Obese and overweight adults had a significantly lower risk of death than those with an ideal body weight, although this is likely biased by reverse causality, as body weight was included as a time-updated variable in our regression analyses. Currently, analyses are underway in our cohort to look in depth at the relationship between weight gain on 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. In addition, other studies have also reported hepatitis B and C virus co-infection[44,45], and the use of tenofovir disoproxil fumarate, atazanavir/ritonavir and lopinavir/ritonavir, to be additional independent predictors of chronic renal impairment[46]. Moreover, renal impairment in the population with HIV is associated with an increased risk of cardiovascular disease[47]. The increase in CKD in our population appears to be largely caused by the increased use of dolutegravir, bictegravir, rilpivirine, and cobicistat, all of which cause reversible inhibition of tubular excretion of creatinine, without causing a true decrease in glomerular filtration.

Non-AIDS-defining malignancies

The most common non-AIDS-defining malignancies (NADM) in the Netherlands are lung, intestinal, anal, 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 [48–52]. 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[53]. 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 NADM (RR 0.62, 95% CI 0.43-0.88, p = 0.008), 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, 3.3% of adults used five or more non-antiretroviral comedications alongside their ART regimen, and this steadily increased to 17.8% of adults in active follow up in 2022. The main drivers behind this increase in polypharmacy are the increasing age of the population and the increase in the number of chronic comorbidities per individual. In adults receiving ART in the period 2007-2021, 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 the first months of 2022 the number of registered SARS-CoV-2 infections and COVID-19-related hospitalizations peaked as the SARS-CoV-2 Omicron variant became dominant in the Netherlands. After the initial Omicron wave the number of registered infections and hospitalizations came down considerably. In 2021, 8 people with HIV were reported to have died as a direct consequence of COVID-19 in the Netherlands. The observed risk factors for severe COVID-19 (hospitalizations and mortality) have remained similar to the risk factors observed in the preceding period: general risk factors, like age, ethnicity and comorbidity continued to be the strongest risk factors for severe COVID-19 in people with HIV in the Netherlands in the Omicron era.

Recommendations

The proportion of individuals dying of AIDS in the Netherlands has markedly declined throughout the ART era, but in order to reach the goal of zero AIDS-deaths by 2027, it is imperative that individuals are identified sooner following infection and rapidly linked to care for an immediate start of ART. This can also be expected to beneficially impact the incidence of comorbidities for which advanced immunodeficiency is a contributing risk factor[54-56]. Of note, our own analyses show a markedly lower risk for non-AIDS malignancies in those who initiate ART within the first year of infection.

The relatively poor five-year survival rates following the diagnosis of several of the analysed non-AIDS-defining comorbidities, compared with survival of all people newly entering care with an AIDS diagnosis, underlines the importance of primary prevention, early diagnosis and aggressive pursuit of treatment and secondary prevention of non-AIDS comorbidities in the population with HIV. Studies in the Netherlands such as the ongoing Comorbidity and Aging with HIV ($AGE_{h}IV$) cohort study[57] and the 2000HIV cohort study[58] have provided further insights into the independent contribution of HIV and HIV-associated factors, such as innate and adaptive immune and coagulation activation, and inflammation. This will hopefully guide the development of interventions that target relevant pathophysiological mechanisms[10,59].

It is important to note that the risk of many, if not each, of the comorbidities frequently identified in people with HIV, is determined by multiple factors. Besides immunodeficiency, additional key contributors for consideration include both well-known traditional, unmodifiable, risk factors such as age and genetic predisposition, and modifiable lifestyle-related factors. But known and potentially unknown effects of antiretroviral therapy and co-infection are risk factors too.

As the population of people with HIV in care in the Netherlands continues to age, the comorbidity burden continues to increase. In tandem with multimorbidity, the risk for polypharmacy is also increasing rapidly in recent years. Both multimorbidity and polypharmacy were each independently associated with an increased risk of death. Adequate prevention and management of comorbidities will become even more important as more people with HIV are entering their 70s and 80s. Polypharmacy should also be adequately managed using tools developed in geriatric medicine (i.e. START/STOPP and Beers), to limit the risk of complex drug-drug interactions, side effects, non-adherence, and other severe adverse health outcomes.

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

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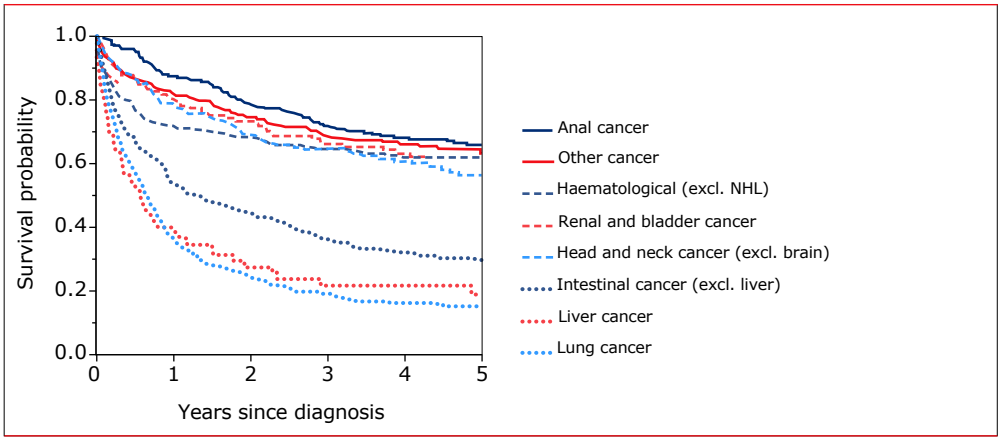
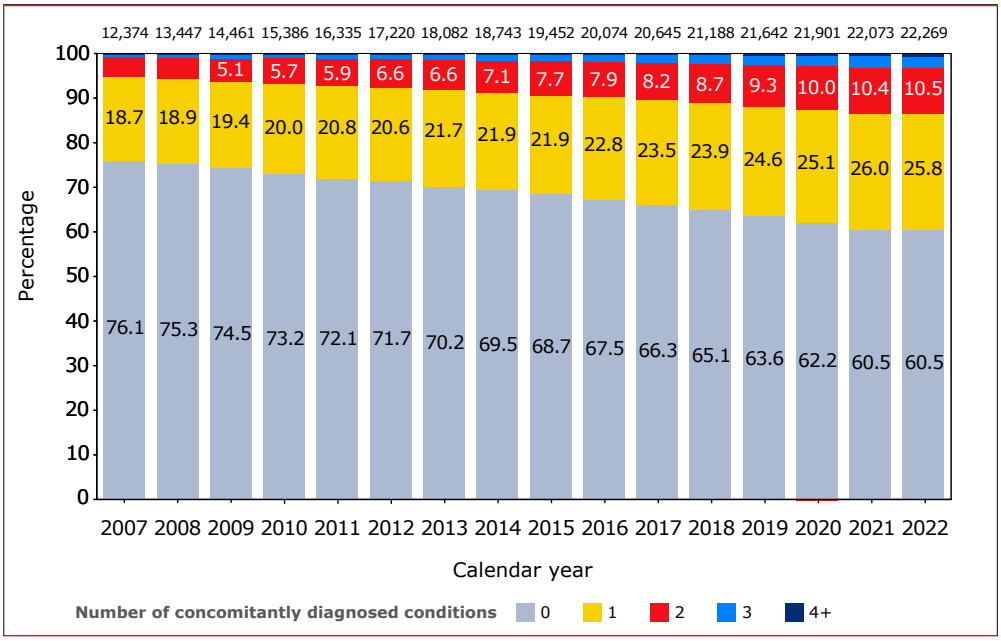
Appendix: supplementary figures and tables

Appendix Figure 3.1: Estimated five-year survival following the diagnosis of the most common non-AIDS-defining malignancies diagnosed between 1 January 2000 and 31 December 2022.

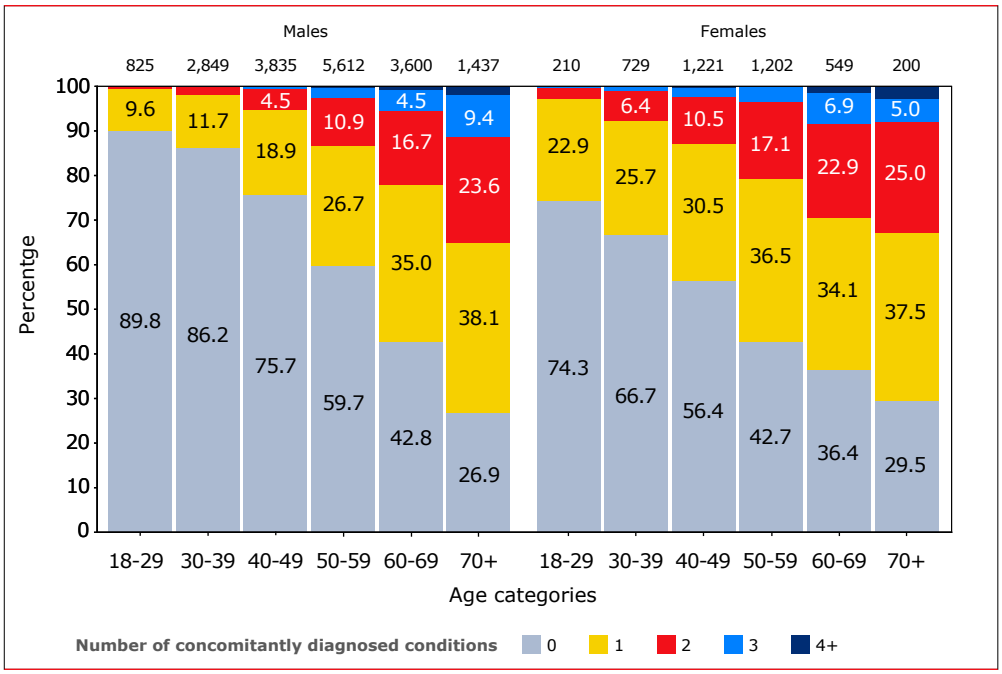


Legend: KM = Kaplan-Meier; excl. = excluding; NHL = non-Hodgkin's lymphoma.

Appendix Figure 3.2: 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 3.3: *Prevalence of non-AIDS multimorbidity by gender in the adult population in 2022. 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 3.1: *Absolute number of causes of death among PWH during the periods 1996–2000, 2001–2005, 2006–2010, and 2011–2022.*

	Calendar period											
Causes of death	**96–00**	**01–05**	**06–10**	**11–15**	**16–22**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**
1. AIDS												
1.1 AIDS – infection	69	120	150	104	35	6	4	4	8	5	3	5
1.2 AIDS – malignancy	60	63	62	44	72	8	13	11	11	6	9	14
1.3 AIDS – unclassifiable	90	63	19	15	32	10	3	4	5	4	4	2
Subtotal	*219*	*246*	*231*	*163*	*139*	*24*	*20*	*19*	*24*	*15*	*16*	*21*
2. Non-AIDS malignancies	30	95	136	194	426	49	62	48	76	70	71	50
3. Cardiovascular disease												
3.1 Myocardial infarction	14	30	46	40	58	8	4	2	10	14	13	7
3.2 Stroke	3	11	13	11	34	7	3	3	2	3	7	9
3.3 Other CVD	6	24	26	50	98	16	10	16	10	11	16	19
Subtotal	*23*	*65*	*85*	*101*	*190*	*31*	*17*	*21*	*22*	*28*	*36*	*35*
4. Non-AIDS infection	23	42	32	27	83	7	3	10	8	16	30	9
5. Liver disease	15	28	55	43	31	6	7	8	.	2	4	4
6. Lung disease	7	11	30	38	80	13	14	9	16	7	11	10
7. Non-natural death												
7.1 Accident or violence	6	11	22	16	25	7	2	4	1	2	4	5
7.2 Suicide	12	30	30	52	67	10	12	11	5	14	8	7
7.3 Euthanasia	7	5	.	2	1	1	.	.	.	.	.	.
Subtotal	*25*	*46*	*52*	*70*	*93*	*18*	*14*	*15*	*6*	*16*	*12*	*12*
8. Alcohol and substance use	12	15	27	18	38	10	4	4	2	4	6	8
9. Other causes	21	24	23	43	101	13	8	18	10	14	21	17
10. Unknown	23	55	51	80	149	19	18	21	14	25	26	26
Total	**398**	**627**	**722**	**777**	**1,330**	**190**	**167**	**173**	**178**	**197**	**233**	**192**

Legend: *CVD = cardiovascular disease.*

Appendix Table 3.2: 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**
Male gender	1.25 (1.10-1.43)	<.001		1.03 (0.88-1.20)	0.753	
Region of birth						
Netherlands	1 (reference)		0.046	1 (reference)		0.106
Other	0.91 (0.83-1.00)	0.047		1.10 (0.98-1.23)	0.105	
HIV-1 transmission route						
Blood contact	0.88 (0.65-1.19)	0.408		0.78 (0.54-1.12)	0.173	
Heterosexual	1.12 (1.00-1.25)	0.043		0.93 (0.80-1.08)	0.338	
IDU	1.62 (1.36-1.93)	<.001		0.72 (0.56-0.92)	0.010	
MSM	1 (reference)		<.001	1 (reference)		0.045
Age *						
18-29	0.90 (0.66-1.23)	0.513	<.001	1.09 (0.89-1.34)	0.392	<.001
30-39	1 (reference)			1 (reference)		
40-49	1.57 (1.35-1.82)	<.001		1.08 (0.95-1.23)	0.229	
50-59	2.76 (2.39-3.20)	<.001		1.27 (1.10-1.46)	0.001	
60-69	5.01 (4.29-5.84)	<.001		1.32 (1.10-1.58)	0.003	
70+	11.62 (9.81-13.76)	<.001		2.02 (1.53-2.68)	<.001	
CD4 cell count **						
0-50	11.65 (9.78-13.87)	<.001	<.001	7.16 (5.80-8.84)	<.001	<.001
50-199	4.60 (4.05-5.21)	<.001		2.84 (2.42-3.33)	<.001	
200-349	1.92 (1.70-2.17)	<.001		1.52 (1.30-1.78)	<.001	
350-499	1.33 (1.17-1.50)	<.001		1.23 (1.05-1.44)	0.011	
500-749	1 (reference)			1 (reference)		
750+	0.84 (0.74-0.95)	0.007		1.07 (0.89-1.28)	0.457	
Per year longer on cART with HIV RNA>1000 cp/mL						
Treatment status	1.06 (1.04-1.07)	<.001	<.001	1.04 (1.02-1.07)	<.001	<.001
Treatment-experienced at start cART	0.95 (0.86-1.04)	0.265		0.64 (0.56-0.72)	<.001	
Treatment-naive at start	1 (reference)			1 (reference)		
Prior AIDS event	1.67 (1.54-1.81)	<.001				
Hepatitis B virus positive	1.23 (1.08-1.40)	0.002		1.08 (0.90-1.30)	0.398	
Hepatitis C virus positive	1.53 (1.34-1.75)	<.001		1.29 (1.08-1.55)	0.006	

			Death			AIDS
Risk factors	**RR (95%CI)**	**p-value**	**Overall p-value**	**RR (95%CI)**	**p-value**	**Overall p-value**
Body mass index *						
<18	3.14 (2.78-3.54)	<.001	<.001			
18-25	1 (reference)					
25-30	0.68 (0.62-0.75)	<.001				
30+	0.86 (0.74-1.00)	0.045				
Smoking status						
Current smoker	1.20 (1.07-1.34)	0.002	<.001	0.80 (0.71-0.90)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	1.96 (1.76-2.18)	<.001		1.02 (0.89-1.17)	0.762	
Early cART ***	0.79 (0.58-1.07)	0.124		1.21 (0.92-1.60)	0.181	

**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 3.3: *Lost to care (no follow up after 31 December 2020) by region of origin and time-updated CD4 cell count.*

	Total			Caribbean			Western Europe / North America		
Last CD4 count	**n**	**PY**	**Incidence/ 1,000 PY (95% CI)**	**n**	**PY**	**Incidence/ 1,000 PY (95% CI)**	**n**	**PY**	**Incidence/ 1,000 PY (95% CI)**
0–50	52	2,850	18.2 (13.6–23.9)	3	216	13.9 (2.9–40.6)	10	165	60.7 (29.1–111.7)
050–199	195	10,464	18.6 (16.1–21.4)	11	707	15.6 (7.8–27.9)	39	1,180	33.1 (23.5–45.2)
200–349	394	24,523	16.1 (14.5–17.7)	14	1,167	12.0 (6.6–20.1)	79	1,972	40.1 (31.7–49.9)
350–499	524	48,089	10.9 (10.0–11.9)	35	1,983	17.7 (12.3–24.6)	118	3,686	32.0 (26.5–38.3)
500–749	737	104908	7.0 (6.5–7.6)	54	5,387	10.0 (7.5–13.1)	194	8,502	22.8 (19.7–26.3)
750+	518	126974	4.1 (3.7–4.4)	31	6,747	4.6 (3.1–6.5)	168	11,429	14.7 (12.6–17.1)

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

	Netherlands			Sub-Saharan Africa			South and south-east Asia		
	n	PY	Incidence/ 1,000 PY (95% CI)	n	PY	Incidence/ 1,000 PY (95% CI)	n	PY	Incidence/ 1,000 PY (95% CI)
	4	1,750	2.3 (0.6–5.9)	29	593	48.9 (32.8–70.3)	6	127	47.4 (17.4–103.2)
	28	6,373	4.4 (2.9–6.3)	109	1,877	58.1 (47.7–70.1)	8	328	24.4 (10.5–48.0)
	74	15,685	4.7 (3.7–5.9)	202	4,721	42.8 (37.1–49.1)	25	979	25.5 (16.5–37.7)
	106	31,582	3.4 (2.7–4.1)	241	8,615	28.0 (24.6–31.7)	24	2,224	10.8 (6.9–16.1)
	211	71,148	3.0 (2.6–3.4)	258	15,525	16.6 (14.7–18.8)	20	4,346	4.6 (2.8–7.1)
	167	89,097	1.9 (1.6–2.2)	135	15,379	8.8 (7.4–10.4)	17	4,322	3.9 (2.3–6.3)

Appendix Table 3.4: *Absolute number of first AIDS events among PWH during the periods 1996–2000, 2001–2005, 2006–2010, 2011–2015 and 2016–2022.*

CDC event	1996–2000	2001–2005	2006–2010	2011–2015	2016–2019	2020–2022	Total	
	N	N	N	N	N	N	N	%
AIDS dementia complex – HIV encephalopathy	40	46	53	43	17	12	211	2.99
Bacterial pneumonia, recurring	48	66	67	78	81	27	367	5.19
CMV colitis/proctitis	1	.	1	2	3	1	8	0.11
CMV disease	27	34	29	34	3	.	127	1.80
CMV esophagitis	.	.	.	.	.	1	1	0.01
CMV meningo-encefalitis	.	.	.	.	1	.	1	0.01
CMV pneumonitis	.	.	.	.	11	15	26	0.37
CMV retinitis	30	20	12	13	11	1	87	1.23
Candidiasis esophagitis	264	237	254	224	114	73	1166	16.50
Candidiasis lungs/bronchial/trachea	7	13	7	6	5	4	42	0.59
Cervical cancer, invasive	3	5	6	4	4	1	23	0.33
Coccidioimycosis, extrapulmonary / disseminated	.	.	1	.	.	.	1	0.01
Cryptococcosis, extrapulmonary / disseminated	21	33	33	11	12	2	112	1.58
Cryptosporidiosis	22	12	11	13	2	2	62	0.88
Cystoisosporiasis	3	9	6	.	.	.	18	0.25
HIV wasting	48	54	76	77	53	24	332	4.70
HSV chronic ulcer	1	3	1	4	19	18	46	0.65
HSV esophagitis	.	.	.	.	.	2	2	0.03
HSV pneumonitis	.	.	.	.	.	1	1	0.01
Herpes simplex virus	32	41	59	38	8	.	178	2.52
Histoplasmosis, extrapulmonary / disseminated	9	12	10	7	2	1	41	0.58
Kaposi sarcoma	154	153	189	138	77	37	748	10.58
Leishmaniasis visceral	.	1	2	2	1	.	6	0.08
Microsporidiosis	11	1	3	1	.	1	17	0.24
Mycobacterium avium/kansasii, extrapulmonary / disseminated	26	20	28	9	7	1	91	1.29
Mycobacterium avium/kansasii, pulmonary	1	2	.	1	8	3	15	0.21
Mycobacterium other / unspecified, extrapulmonary / disseminated	20	13	8	10	2	1	54	0.76
Mycobacterium other / unspecified, pulmonary	.	3	5	9	4	1	22	0.31
Non-Hodgkin`s lymphoma (NHL)	57	88	79	99	55	28	406	5.75
Penicilliosis	.	.	1	.	.	.	1	0.01
Pneumocystis jirovecii extrapulmonary	1	1	3	.	1	.	6	0.08

CDC event	1996–2000	2001–2005	2006–2010	2011–2015	2016–2019	2020–2022	Total	
	N	N	N	N	N	N	N	%
Pneumocystis jirovecii pneumonia	331	302	327	268	165	96	1489	21.07
Primary CNS lymphoma	8	4	9	6	4	.	31	0.44
Progressive multifocal leukoencephalopathy	18	25	35	24	6	4	112	1.58
Salmonella sepsis, recurring	2	.	.	1	.	.	3	0.04
Toxoplasmosis of the brain	69	100	57	43	25	11	305	4.32
Tuberculosis, extrapulmonary / disseminated	80	114	81	55	22	15	367	5.19
Tuberculosis, pulmonary	105	177	118	80	47	15	542	7.67
Total	**1439**	**1589**	**1571**	**1300**	**770**	**398**	**7067**	**100**

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

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

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
Male gender	1.20 (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 3.6: *Specific CDC-B and CDC-C (AIDS) events occurring in individuals on ART with undetectable viral load between 2000 and 2022.*

		All events		0-50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Aspergillosis, invasive pulmonary	12	0.4%	1	0.4%
	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis oropharyngeal	833	26.1%	71	27.3%
	Candidiasis vulvovaginal, frequent/persistent	56	1.8%	1	0.4%
	Cardiomyopathy, HIV-related	6	0.2%	0	0.0%
	Cardiomyopathy, with HIV-related component	21	0.7%	1	0.4%
	Diarrhea, HIV-related >=30 days	63	2.0%	1	0.4%
	Fever e.c.i. / HIV-related	6	0.2%	0	0.0%
	HIV-associated nephropathy (HIVAN)	22	0.7%	1	0.4%
	Herpes zoster, multidermatomal	24	0.8%	3	1.2%
	Herpes zoster, recurring / multidermatomal unspecified	202	6.3%	6	2.3%
	Herpes zoster, unidermatomal recurrent	45	1.4%	3	1.2%
	Listeriosis	1	0.0%	0	0.0%
	Myelopathy, HIV-related	10	0.3%	0	0.0%
	Neuropathy, HIV-related	117	3.7%	2	0.8%
	Neuropathy, with HIV-related component	101	3.2%	2	0.8%
	Nocardiosis	2	0.1%	1	0.4%
	Oral Hairy Leucoplakia (OHL)	55	1.7%	1	0.4%
	Pelvic inflammatory disease	9	0.3%	0	0.0%
	Thrombocytopenia, HIV-related	116	3.6%	4	1.5%
	Thrombocytopenia, with HIV-related component	20	0.6%	3	1.2%
	Weight loss >10%, HIV-related / unknown cause	35	1.1%	2	0.8%
Subtotal		1757	55.0%	103	39.6%

CD4 category										
	050–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
3	0.5%	1	0.2%	1	0.2%	3	0.5%	3	0.7%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
200	32.6%	162	25.0%	137	22.9%	152	23.0%	111	26.7%
5	0.8%	9	1.4%	18	3.0%	18	2.7%	5	1.2%
2	0.3%	0	0.0%	2	0.3%	1	0.2%	1	0.2%
4	0.7%	2	0.3%	2	0.3%	8	1.2%	4	1.0%
6	1.0%	16	2.5%	10	1.7%	22	3.3%	8	1.9%
1	0.2%	2	0.3%	0	0.0%	1	0.2%	2	0.5%
4	0.7%	3	0.5%	5	0.8%	4	0.6%	5	1.2%
0	0.0%	5	0.8%	2	0.3%	9	1.4%	5	1.2%
24	3.9%	50	7.7%	44	7.4%	48	7.3%	30	7.2%
6	1.0%	3	0.5%	4	0.7%	13	2.0%	16	3.8%
0	0.0%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
4	0.7%	2	0.3%	0	0.0%	1	0.2%	3	0.7%
8	1.3%	15	2.3%	29	4.8%	37	5.6%	26	6.3%
9	1.5%	11	1.7%	27	4.5%	33	5.0%	19	4.6%
0	0.0%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
13	2.1%	12	1.9%	9	1.5%	11	1.7%	9	2.2%
0	0.0%	4	0.6%	0	0.0%	3	0.5%	2	0.5%
22	3.6%	27	4.2%	24	4.0%	27	4.1%	12	2.9%
2	0.3%	9	1.4%	0	0.0%	5	0.8%	1	0.2%
5	0.8%	8	1.2%	6	1.0%	8	1.2%	6	1.4%
319	52.0%	343	52.9%	320	53.5%	404	61.0%	268	64.4%

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
CDC-C events	AIDS dementia complex – HIV encephalopathy	46	1.4%	5	1.9%
	Bacterial pneumonia, recurring	334	10.4%	14	5.4%
	CMV disease	19	0.6%	4	1.5%
	CMV esophagitis	2	0.1%	1	0.4%
	CMV pneumonitis	1	0.0%	0	0.0%
	CMV retinitis	19	0.6%	4	1.5%
	Candidiasis esophagitis	255	8.0%	25	9.6%
	Candidiasis lungs/bronchial/trachea	11	0.3%	2	0.8%
	Cervical cancer, invasive	13	0.4%	1	0.4%
	Coccidioimycosis, extrapulmonary / disseminated	1	0.0%	0	0.0%
	Cryptococcosis, extrapulmonary / disseminated	16	0.5%	6	2.3%
	Cryptosporidiosis	11	0.3%	4	1.5%
	Cystoisosporiasis	2	0.1%	0	0.0%
	HIV wasting	17	0.5%	5	1.9%
	HSV chronic ulcer	38	1.2%	2	0.8%
	HSV esophagitis	2	0.1%	0	0.0%
	HSV pneumonitis	2	0.1%	0	0.0%
	Herpes simplex virus	61	1.9%	6	2.3%
	Histoplasmosis, extrapulmonary / disseminated	4	0.1%	3	1.2%
	Kaposi sarcoma	122	3.8%	8	3.1%
	Leishmaniasis visceral	5	0.2%	1	0.4%
	Microsporidiosis	5	0.2%	2	0.8%
	Mycobacterium avium/kansasii, extrapulmonary / disseminated	25	0.8%	5	1.9%
	Mycobacterium avium/kansasii, pulmonary	3	0.1%	0	0.0%
	Mycobacterium other / unspecified, extrapulmonary / disseminated	10	0.3%	3	1.2%
	Mycobacterium other / unspecified, pulmonary	5	0.2%	0	0.0%
	Non-Hodgkin`s lymphoma (NHL)	164	5.1%	7	2.7%
	Pneumocystis jirovecii extrapulmonary	1	0.0%	0	0.0%
	Pneumocystis jirovecii pneumonia	73	2.3%	23	8.8%
	Primary CNS lymphoma	6	0.2%	1	0.4%
	Progressive multifocal leukoencephalopathy	20	0.6%	6	2.3%
	Toxoplasmosis of the brain	22	0.7%	9	3.5%
	Tuberculosis, extrapulmonary / disseminated	51	1.6%	4	1.5%
	Tuberculosis, pulmonary	74	2.3%	6	2.3%
Subtotal		**1440**	**45.0%**	**157**	**60.4%**
Total		**3197**	**100.0%**	**260**	**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	1.0%	8	1.2%	11	1.8%	8	1.2%	8	1.9%
53	8.6%	79	12.2%	83	13.9%	68	10.3%	37	8.9%
1	0.2%	4	0.6%	6	1.0%	1	0.2%	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%	1	0.2%
4	0.7%	6	0.9%	4	0.7%	1	0.2%	0	0.0%
63	10.3%	55	8.5%	43	7.2%	41	6.2%	28	6.7%
1	0.2%	5	0.8%	1	0.2%	1	0.2%	1	0.2%
3	0.5%	1	0.2%	2	0.3%	5	0.8%	1	0.2%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
5	0.8%	3	0.5%	1	0.2%	1	0.2%	0	0.0%
0	0.0%	1	0.2%	3	0.5%	2	0.3%	1	0.2%
1	0.2%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
8	1.3%	1	0.2%	2	0.3%	1	0.2%	0	0.0%
7	1.1%	4	0.6%	3	0.5%	14	2.1%	8	1.9%
1	0.2%	0	0.0%	1	0.2%	0	0.0%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	0.5%
6	1.0%	13	2.0%	17	2.8%	15	2.3%	4	1.0%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
11	1.8%	27	4.2%	28	4.7%	32	4.8%	16	3.8%
3	0.5%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
2	0.3%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
10	1.6%	5	0.8%	3	0.5%	1	0.2%	1	0.2%
0	0.0%	1	0.2%	0	0.0%	1	0.2%	1	0.2%
3	0.5%	3	0.5%	0	0.0%	1	0.2%	0	0.0%
2	0.3%	0	0.0%	2	0.3%	1	0.2%	0	0.0%
42	6.9%	39	6.0%	37	6.2%	27	4.1%	12	2.9%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
24	3.9%	11	1.7%	7	1.2%	6	0.9%	2	0.5%
2	0.3%	2	0.3%	1	0.2%	0	0.0%	0	0.0%
6	1.0%	4	0.6%	2	0.3%	2	0.3%	0	0.0%
7	1.1%	4	0.6%	1	0.2%	1	0.2%	0	0.0%
10	1.6%	7	1.1%	5	0.8%	13	2.0%	12	2.9%
13	2.1%	21	3.2%	15	2.5%	12	1.8%	7	1.7%
294	**48.0%**	**305**	**47.1%**	**278**	**46.5%**	**258**	**39.0%**	**148**	**35.6%**
613	**100.0%**	**648**	**100.0%**	**598**	**100.0%**	**662**	**100.0%**	**416**	**100.0%**