Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

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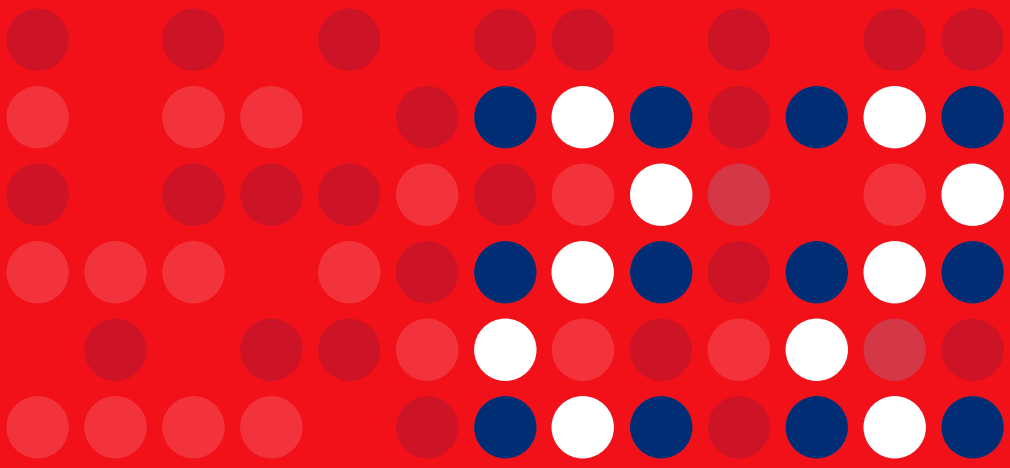
Chapter 3: Morbidity and mortality



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; in a subgroup of recently-diagnosed, effectively-treated individuals, it was shown to be similar to that of the general population in the Netherlands[1]. Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased[2], morbidity and/or mortality associated with non-AIDS-related diseases has increased among PWH during the ART era[3–8]. 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 morbidity may be higher in individuals with HIV treated with ART, than in HIV-negative individuals of comparable age[9-11]. For example pulmonary hypertension[12], bone disease, and non-traumatic bone fractures[13-15] have each been reported to be more common in PWH. There is also a concern that HIV-related neurocognitive impairment may persist, or even progress, despite otherwise effective long-term ART[16-18]. Just as with HIV-negative individuals, traditional risk factors (such as tobacco use[19], alcohol abuse, and viral hepatitis co-infection[20]) also contribute to the increased risk of certain non-AIDS 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[21,22].

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 28,240 adult individuals ever registered by SHM – that breaks down as 27,760 adults and an additional 479 individuals who were diagnosed with HIV as children and have since become adults. In addition, we report on the incidence of AIDS and non-AIDS comorbidities, particularly diabetes mellitus, cardiovascular disease, chronic kidney disease (CKD), and non-AIDS malignancies in PWH.

Definitions

AIDS is defined as having experienced any of the United States' Centers for Disease Control (CDC) category C conditions[23]. 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 2016-20. We standardised these estimates according to the age distribution of the population during the period 2016-20 (divided into the following age classes: 18-29, 30-39, 40-49, 50-59, 60-69, and 70 years and over), using the indirect method[24]. Indirect standardisation compares the incidence rates in the study and reference (period: 2016-20) populations by applying the stratum-specific rates in the reference population to the study population. We investigated risk factors for AIDS, death,

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

The baseline for treated and untreated 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/mm3;
- 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 29,039 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 7.4-10.5) per 1,000 PYFU in 2010. It has since remained stable at that 2010 level up to 2020, but the observed mortality rate had increased slightly to 11.2 (9.8-12.9) in 2021 (*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 5.5 per 1,000 PYFU in 2021.

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 8.4 (7.2-9.9) per 1,000 PYFU in 2020, and 10.2 (8.7-11.9) in 2021. *Appendix Figure 3.1* shows the five-year survival curves after diagnosis of the first AIDS-defining condition, compared to survival for all people with HIV as well as survival after diagnosis of several common, non-AIDS-defining comorbidities.

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 HIV-positive individuals who present late for care with advanced immune deficiency. As such, the rate still falls short of the aim of zero AIDS-deaths by 2022, as stated in the Netherlands' National Action Plan on STIs, HIV and Sexual Health[25]. *Table 3.1* shows the characteristics of adults with HIV who died of AIDS, compared to those who died of non-AIDS causes in the period 2012-21. 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 62.9% 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 57% of cases, they did not have controlled viremia, and 15.5% 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 3.2*), primarily as a consequence of the ever increasing size and average age of the population of people with HIV in the Netherlands. People with HIV that were born in the Netherlands, MSM and men in general are overrepresented among those who died of non-AIDS causes, because people in these three (overlapping) categories have a higher average age compared to migrants, HIV transmission categories other than MSM, and women. Independent risk factors for death and for being diagnosed with an AIDS-defining condition are listed in *Appendix Table 3.2*.

Table 3.1: Characteristics of adults with HIV who died of AIDS compared to adults with HIV who died of non-AIDS causes in the period 2012-21.

	Died of non-AIDS causes	Died of AIDS	p-value
Number of subjects	1487 (86.5%)	232 (13.5%)	
Age	59.1 (51.2-67.9)	54 (45.1-61.8)	<.001
Male gender	1293 (87.0%)	188 (81.0%)	0.019
Dutch origin	1058 (71.1%)	143 (61.6%)	0.004
MSM	843 (56.7%)	106 (45.7%)	0.002
Heterosexual transmission	390 (26.2%)	78 (33.6%)	0.021
Other transmission categories	254 (17.1%)	48 (20.7%)	0.194
Years since HIV diagnosis	15 (8.26-21.6)	6.6 (0.69-13.6)	<.001
Years since start ART	12.3 (6.08-17.6)	2.87 (0.34-11.9)	<.001
CD4 at HIV diagnosis	290 (111-510)	115 (30-315)	<.001
Late presenter (CD4<350 at entry in care	831 (56.0%)	178 (78.1%)	<.001
Very late presenter (CD4<200)	545 (36.7%)	146 (62.9%)	<.001
CD4 nadir	140 (50-252)	50 (12-110)	<.001
Last CD4 measured before death	480 (290-690)	140 (43-310)	<.001
Not undetectable at date of death	228 (15.4%)	126 (56.5%)	<.001
Not on ART at date of death	102 (6.9%)	36 (15.5%)	<.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) Annual mortality and (B) incidence of AIDS in 29,039 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.*

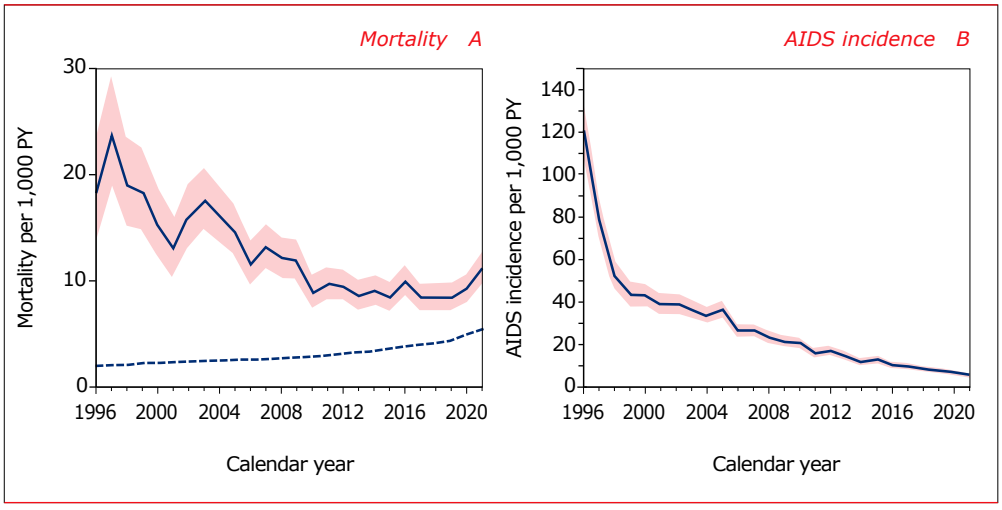
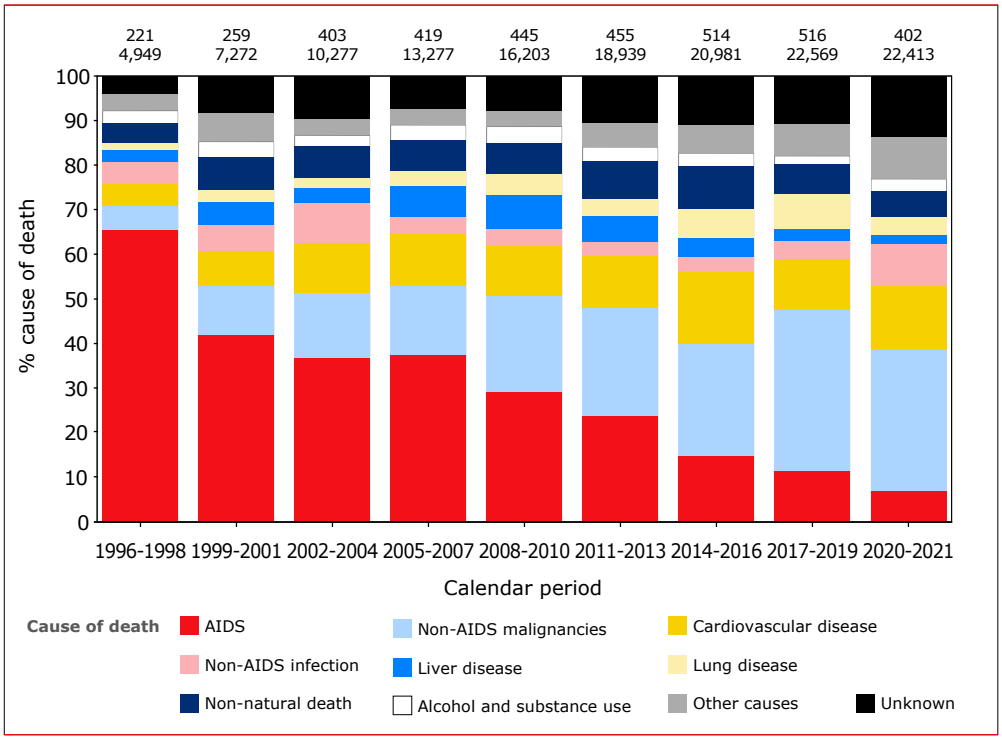


Figure 3.2: Relative changes in causes of death in different calendar periods since the introduction of combination antiretroviral therapy (ART) in the Netherlands. The numbers at the top of each bar represent the total number of deaths and the total number of individuals that were at risk during that 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 2021 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[26].

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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 2021, a total of 151 instances of euthanasia were recorded; 30% of cases occurred in patients who died of AIDS, 40% in patients who died of non-AIDS-defining malignancies, and the remaining 30% in patients who died of other diseases. Our definition of euthanasia does not include the use of standard practice palliative care, such as palliative sedation in the terminal phase of the underlying disease.

AIDS-defining events

In the group of 29,039 adult PWH ever registered in the SHM database, the incidence of first AIDS-defining events decreased sharply from 121.0 (95% CI 108.5-134.6) in 1996 to 5.7 (4.7-6.9) cases per 1,000 PYFU in 2021 (*Figure 3.1B*). *Appendix Table 3.4* gives an overview of the first AIDS-defining events occurring between 1996 and 2021. The most common first AIDS-defining events between 2016 and 2021 were:

- *Pneumocystis jirovecii* pneumonia (21% of all events);
- oesophageal candidiasis (17%);
- Kaposi's sarcoma (11%);
- tuberculosis (pulmonary 8%, extrapulmonary 5%);
- lymphoma (6%);
- recurrent bacterial pneumonia (5%);
- AIDS-related wasting (5%);
- toxoplasmosis of the brain (4%);
- AIDS dementia complex/HIV encephalopathy (3%); and
- cytomegalovirus-associated end organ disease (3%).

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

In the present analyses, we concentrate on the first occurrence of any AIDS-defining event after the start of 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 2021, 25,684 individuals contributed a total of 224.9 thousand PYFU, during which 3,013 CDC-B and/or CDC-C (AIDS-defining events) were diagnosed. This resulted in an incidence rate of 12.4 events per 1,000 PYFU (1,647 CDC-B events, 6.8 events/1,000 PYFU; 1,366 CDC-C/AIDS events, 5.6 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 10.7 and 5.5 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 2.9 (95% CI 2.6-3.2) and 1.8 (1.5-2.1) events/1,000 PYFU, respectively. Note that the incidence in the over 750 cells/mm^3 stratum is statistically significantly lower than in the 500-749 cells/mm^3 stratum. In these highest CD4 strata, the main AIDS-defining events that still occurred were:

- recurrent bacterial pneumonia;
- Kaposi's sarcoma;
- oesophageal candidiasis;
- non-Hodgkin's lymphoma;
- tuberculosis (pulmonary and extrapulmonary);
- 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 2021 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)
0-49	252	101	151	0.6	456 (401-516)	183 (149-222)	273 (231-320)
50-199	581	304	277	8.6	67.7 (62.3-73.4)	35.4 (31.5-39.6)	32.3 (28.6-36.3)
200-349	636	341	295	27.6	23.0 (21.3-24.9)	12.4 (11.1-13.7)	10.7 (9.51-12.0)
350-499	563	295	268	48.4	11.6 (10.7-12.6)	6.10 (5.42-6.83)	5.54 (4.90-6.24)
500-749	623	375	248	85.4	7.30 (6.73-7.89)	4.39 (3.96-4.86)	2.90 (2.55-3.29)
750+	358	231	127	71.6	5.00 (4.49-5.54)	3.22 (2.82-3.67)	1.77 (1.48-2.11)
Total	**3013**	**1647**	**1366**	**242.2**	**12.4 (12.0-12.9)**	**6.80 (6.48-7.14)**	**5.64 (5.35-5.95)**

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 2021 a cumulative total of 1,125 cases of tuberculosis were diagnosed in 939 individuals, of which 656 (58.3%) were pulmonary cases and 469 (41.7%) were extrapulmonary/disseminated tuberculosis cases. During that same period, 531 cases of other mycobacterial infections were diagnosed in 473 individuals: 21 pulmonary and 304 extrapulmonary M. avium or M. kansasii cases, and 57 pulmonary and 149 extrapulmonary / disseminated cases of other atypical mycobacterial infections. *Figures 3.3A & 3.3B* 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 (50.4%) or from south(-east) Asia (8.9%) were strongly overrepresented among the tuberculosis cases, while those of Dutch origin (16.5%) and people from other western European countries (3.8%) were underrepresented. People originating from central and eastern European countries represented 3.4% and 1.6% of tuberculosis cases. Region of origin was not strongly associated with 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

Five per cent of the individuals diagnosed with pulmonary tuberculosis and 4.5% of the individuals diagnosed with extrapulmonary tuberculosis died within 365 days of the diagnosis, with the reported cause of death being 'AIDS' or 'infection'. The disease-related mortality rates within 365 days of diagnosis were:

- 0% for pulmonary and 16.8% for extrapulmonary M. avium / kansasii infections;
- 7.0% for pulmonary and 20.8% 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.

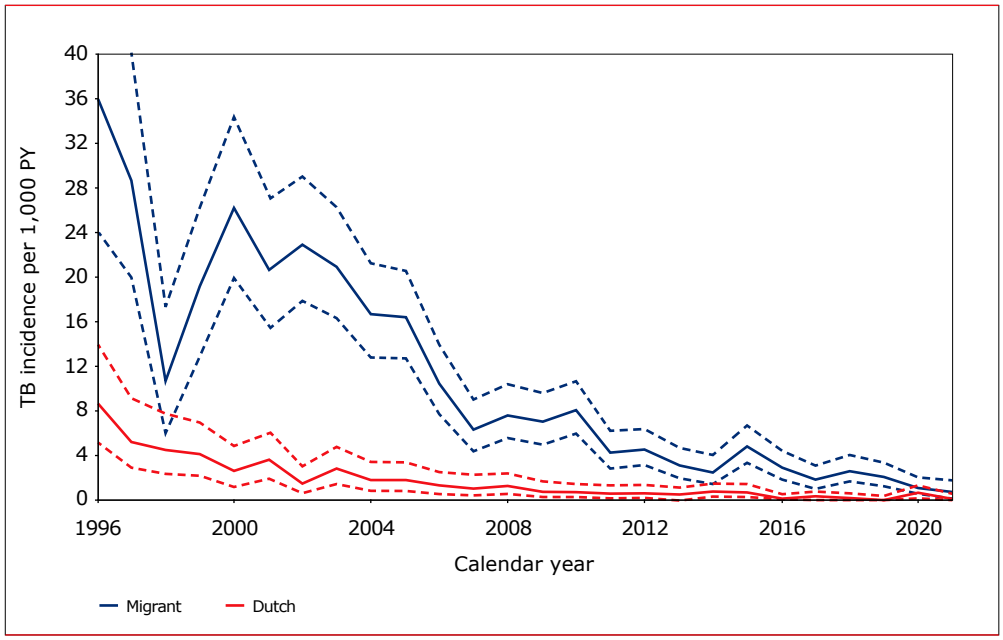
SHM has been collecting data on LTBI screening and treatment since 2018. IGRA testing during an episode in which active TB was diagnosed, was excluded from this dataset. A limitation of our analysis of LTBI screening is that we do not have data on whether, at the time of IGRA testing, the individual had complaints that may have been caused by tuberculosis, which then prompted the treating physician to perform IGRA testing. In 22.6% 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 1,534 individuals. In 142 (9.3%) of these individuals LTBI testing was positive, and 56 (39.4%) of those received a course of LTBI treatment. LTBI treatment consisted of:

- isoniazid plus rifampicin (typically for a duration of three months) in 15 individuals;
- isoniazid monotherapy (typically for a duration of six to nine months) in 32 individuals; and
- rifampicin monotherapy (typically for a duration of four months) in three individuals.

A further six individuals received another non-standard treatment. In the 142 individuals who tested positive on LTBI screening, one case of active extrapulmonary tuberculosis developed (four months after diagnosis) while that individual was receiving treatment consisting of rifampicin plus isoniazid. Of the 86 individuals with positive LTBI screening who did not receive LTBI treatment, 15 (17.4%) were known to have been diagnosed with and treated for active tuberculosis prior to the LTBI screening.

Figure 3.3A & 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).



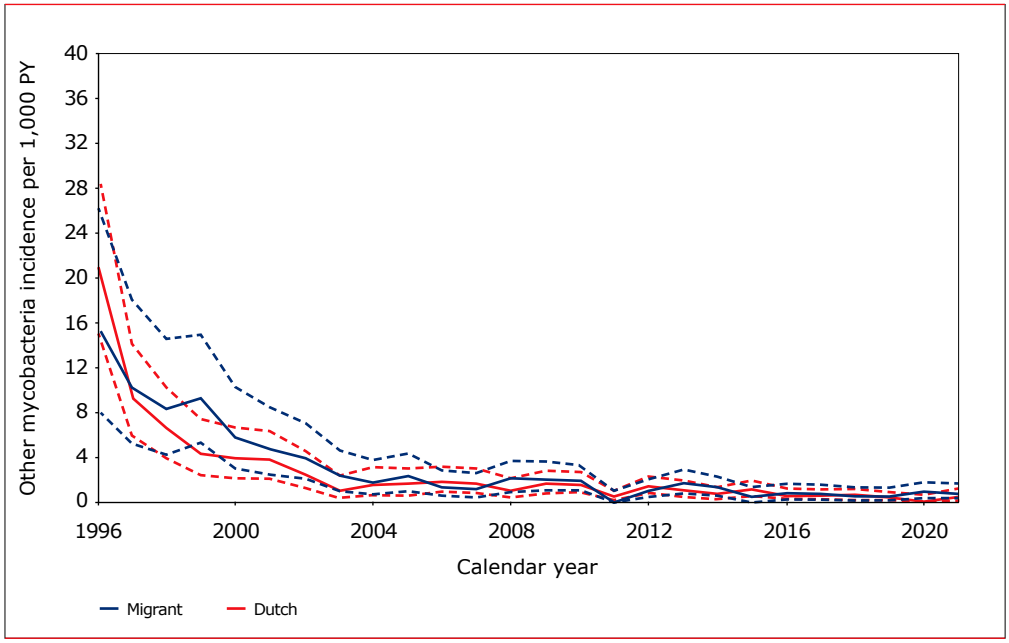


Table 3.3: Characteristics at the time individuals were diagnosed with tuberculosis or other mycobacterial infections for the first time.

	Tuberculosis	Other mycobacterial infections	p-value
Number of subjects	939 (66.5%)	473 (33.5%)	
Age	36.8 (30.5-44.6)	40 (34.5-47.5)	<.001
Male gender	625 (66.6%)	380 (80.3%)	<.001
Dutch origin	176 (18.7%)	270 (57.1%)	<.001
MSM	209 (22.3%)	218 (46.1%)	<.001
Heterosexuals	535 (57.0%)	182 (38.5%)	<.001
Other risk groups	195 (20.8%)	73 (15.4%)	0.018
Years since HIV diagnosis	0.91 (0.5- 4.5)	1.16 (0.61-6.55)	<.001
Years since start ART	0.41 (0-0.99)	0.63 (0.26- 1.3)	<.001
CD4 at HIV diagnosis	190 (60-400)	40 (10-197)	<.001
Late presenter (CD4<350 at entry in care	430 (69.0%)	356 (84.8%)	<.001
Very late presenter (CD4<200)	633 (67.4%)	368 (77.8%)	<.001
CD4 nadir	110 (40-242)	20 (10- 50)	<.001
Last CD4 measured before event	210 (100-370)	90 (23-180)	<.001
Not undetectable at date of event	774 (82.4%)	360 (76.1%)	0.006
Not on ART at date of event	682 (72.6%)	229 (48.4%)	<.001

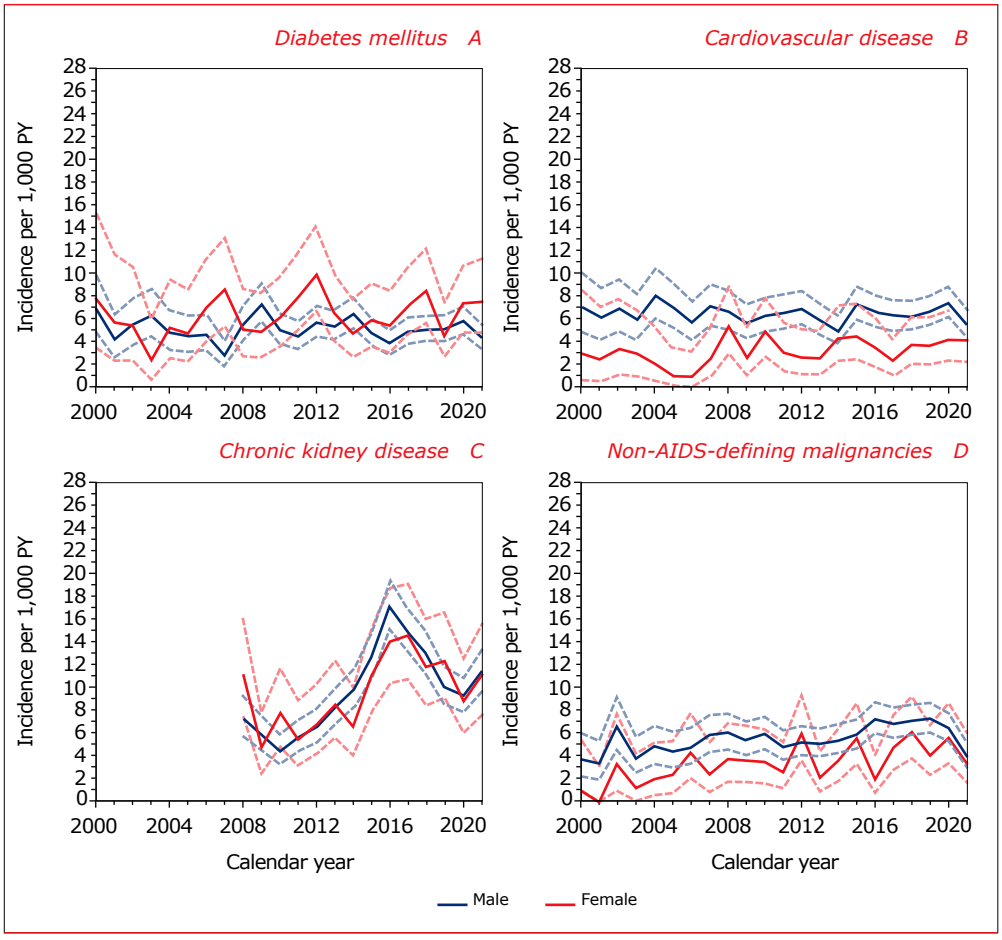
Non-AIDS-defining events

Of the 29,039 adult PWH ever registered with SHM, 28,695 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 (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 3.4*).

Figure 3.4: *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 28,695 individuals aged 18 years and over who were in follow up in, or after, January 2000, a total of 1,624 (n=1,248 men and n=376 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.4A*), and in 2021 was 4.3 (95% CI 3.3-5.6) per 1,000 PYFU in men and 7.5 (4.7-11.2) per 1,000 PYFU in women. In men, the age-standardised incidence ratio declined over time and was significantly lower in 2016-21 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 2016-21 (*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; and
- a prior AIDS diagnosis (*Appendix Table 3.5*).

Moreover, the risk of new-onset diabetes in the periods 2000-10 and 2011-15 was significantly higher than in the period 2016-21. A longer time on didanosine was also significantly associated with an increased risk.

Table 3.4: *Crude incidence of diabetes mellitus per 1,000 person years of follow up in 2000–10, 2011–15 and 2016–21 and age-standardised incidence ratio (indirect method) with 95% confidence intervals.*

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)
2000–2010	5.2 (4.7–5.7)	1.40 (1.27–1.54)	5.8 (4.8–6.9)	0.99 (0.82–1.16)
2011–2015	5.3 (4.8–5.9)	1.24 (1.11–1.37)	6.9 (5.7–8.3)	1.09 (0.89–1.30)
2016–2021	4.9 (4.4–5.3)	1 (reference)	6.7 (5.7–8.0)	1 (reference)

**Standardised according to the observed age distribution between 2016–21.*

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

Cardiovascular disease

From January 2000 onwards, 1,759 individuals (n=1,566 men and n=193 women) had a fatal or non-fatal cardiovascular event. Of these:

- 874 had a myocardial infarction;
- 635 had a stroke;
- 134 had a coronary artery bypass graft;
- 630 had a coronary angioplasty or stenting; and
- 14 had a carotid endarterectomy.

The crude incidence over time remained stable and was lower in women than in men (*Figure 3.4B*). The 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 and past smoking; and
- the presence of hypertension.

Estimated cardiovascular risk using the D:A:D algorithm was also higher during 2000-10 and 2011-15 than during 2016-21, independent of other variables included in the analysis (*Appendix Table 3.5*). The strong positive association between use of abacavir and CVD was independent of renal function. When eGFR, estimated using the Cockcroft-Gault method (available from 2007 onwards), was included in the model the abacavir effect was only slightly attenuated, decreasing from an incidence risk ratio (IRR) of 1.58 to 1.43, $p<0.001$. 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 1.08 (95% CI 0.95-1.23), p = 0.22;
- at 30-60 ml/min the IRR was 1.65 (1.36-2.00), p<0.001;
- at 15-30 ml/min, the IRR was 4.82 (3.37-6.90), p<0.001; and
- at 0-15 ml/min the IRR was 3.80 (2.22-6.52), p<0.001.

From January 2000 onwards, 229 men and 23 women experienced a fatal or non-fatal secondary cardiovascular event (n=141 myocardial infarction, n=119 stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2021 in men and women with a prior cardiovascular event was 27.1 (23.7-30.8) and 19.9 (12.6-29.8), respectively. The crude rate and age-standardised incidence ratio (SIR; indirect method) of secondary myocardial infarction and stroke per 1,000 PYFU changed significantly during 2000-10 (crude rate: 30.1 events per 1,000 PYFU; SIR: 1.24, 95% CI 0.96-1.51), but not during 2011-15 (crude rate: 24.3 events per 1,000 PYFU; SIR: 0.98, 95% CI 0.74-1.22) compared with the reference period 2016-20 (crude rate: 25.1 events per 1,000 PYFU).

Table 3.5: *Crude incidence of cardiovascular disease per 1,000 person years of follow up in 2000–10, 2011–15, and 2016–21 and age-standardised incidence ratio with 95% confidence intervals.*

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)
2000–2010	6.5 (6.0–7.1)	1.52 (1.39–1.65)	2.9 (2.2–3.6)	1.40 (1.06–1.74)
2011–2015	6.3 (5.7–6.9)	1.19 (1.07–1.30)	3.3 (2.5–4.4)	1.18 (0.87–1.49)
2016–2021	6.4 (5.9–6.9)	1 (reference)	3.5 (2.7–4.4)	1 (reference)

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

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

Trends in cardiovascular risk factors

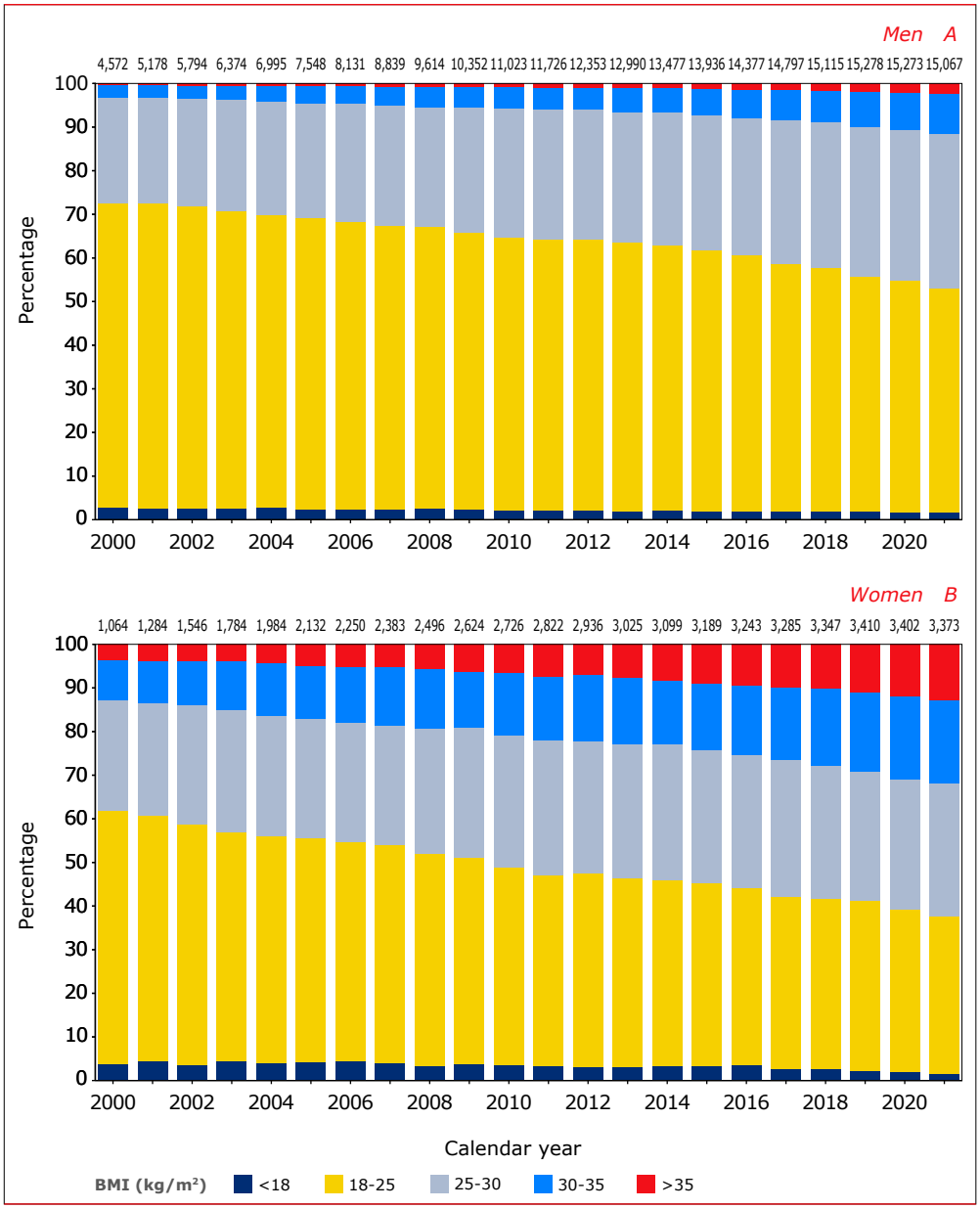
Figures 3.5A and *3.5B* show that the distribution of body mass index (BMI) of both men and women in the HIV-1-positive population has increased over time. In 2021, the proportion of men with available BMI data who were overweight (25-30 kg/m^2) or obese (WHO class I: 30-35 kg/m^2 and WHO class II/III: 35 kg/m^2 or over), was 35.6%, 9.3% and 2.3%, respectively. In women, these proportions were 30.6%, 18.9% and 12.8%, respectively.

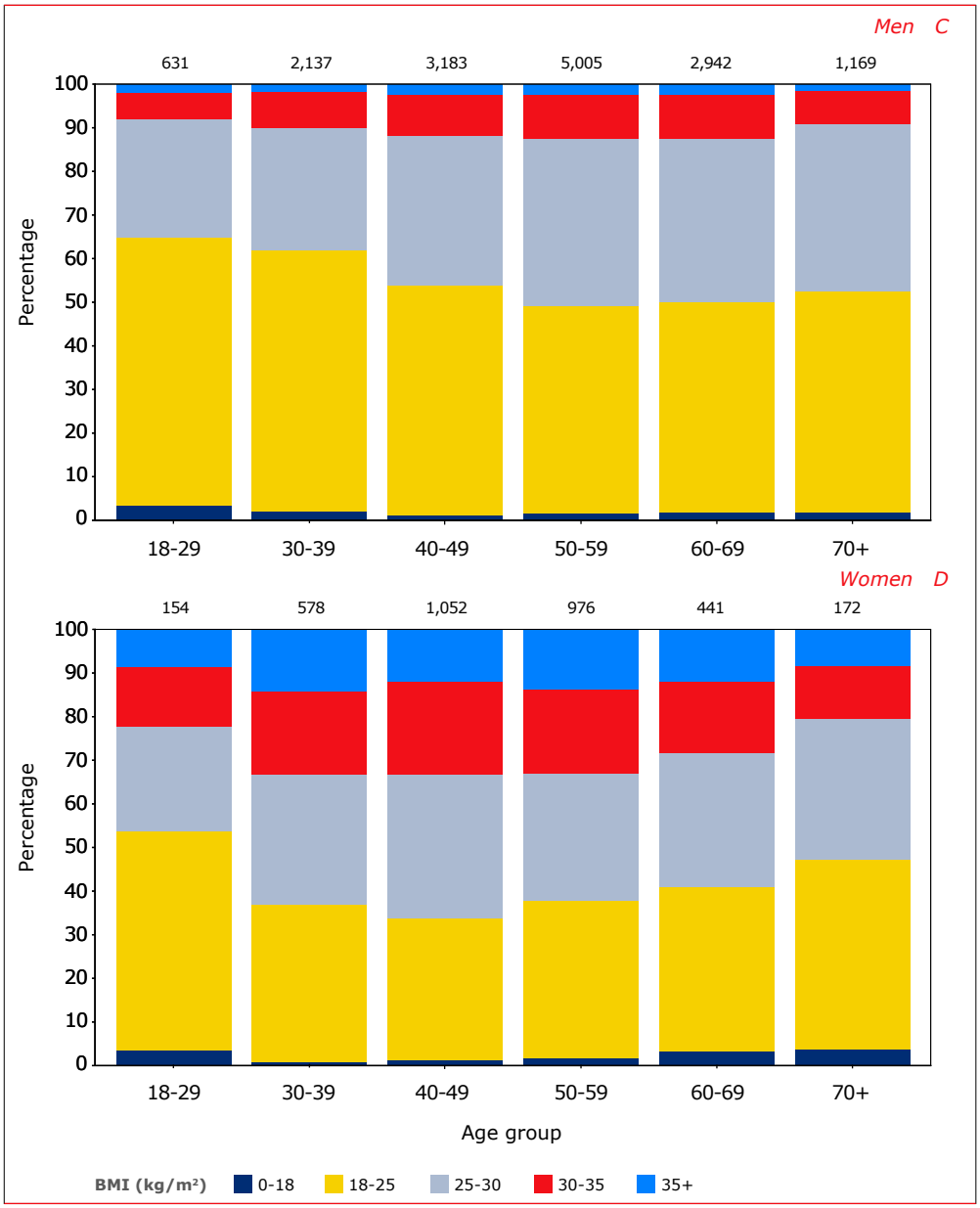
Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the population with HIV. This analysis revealed that the increase was at least partially driven by changes over time in population demographic 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. *Figures 3.5C* and *3.5D* show the distribution of BMI according to age groups in 2021 for men and women. Whereas in adult men of all age groups, the proportion classified as obese (11.6%) was somewhat lower than the proportion found in the general Dutch male population (12.3%), in women of all age groups there was more obesity (31.7%) than in the general Dutch female population (15.4%)[27]. There were substantial differences between those of Dutch origin, Western migrants and non-Western migrants: among males, 10.3% of Dutch men, 12.4% of Western migrants and 14.7% of non-Western migrants were obese. In females, however, those figures were 21.8%, 20.5%, and 38.4%, respectively. Being obese (a BMI over 30) was independently associated with an increased risk of diabetes (IRR 5.43, 95% CI 4.67-6.31, p<0.001), but that was not the case with CVD, CKD or non-AIDS-defining malignancies (*Appendix Table 3.5*).

Figure 3.6A shows that, in 2021, 51.3% of those treated with antihypertensives still had grade 1 hypertension or higher. In 2021, 27.3% (4,424) of individuals not using antihypertensives had grade 1-3 hypertension (*Figure 3.6B*). For 4,151 (93.8%) of these individuals, a five-year cardiovascular disease (CVD) risk could be calculated with the recalibrated D:A:D study algorithm[28]: 267 (6.4%) had a five-year CVD risk of 10% or more. According to the European AIDS Clinical Society (EACS) guidelines these individuals, in particular, should receive antihypertensive treatment[29]. *Figure 3.7* gives an overview of the ART-treated population's estimated risk of CVD over time. In 2000, the percentage of individuals at high (5-10%) or very high (10% or more) five-year risk were 12.0% and 5.8%, respectively, which steadily increased to 21.3% and 14.1%, respectively, in 2021. The increase in the percentage of individuals at high or very high risk likely reflects the increasing age of the study population.

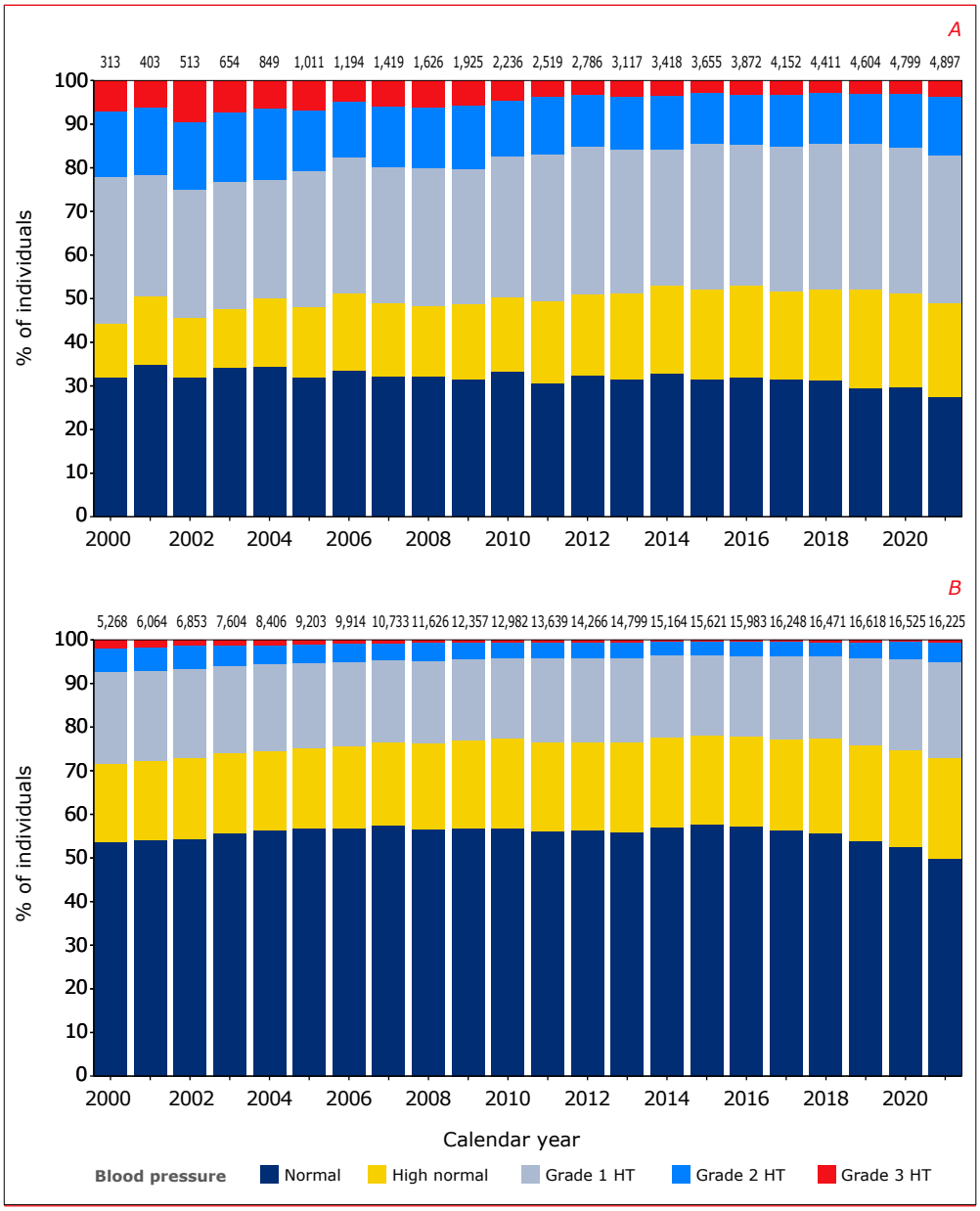
Figure 3.5: Distribution of the body mass index (BMI) at the end of each calendar year in (A) men, and (B) women, as a percentage of the total number of men and women with a known BMI in each year, and distribution of the BMI over the age groups for (C) men, and (D) women, in 2021. For each individual, the last available weight measurement in each year was selected. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year (A & B) or from that age group (C & D).





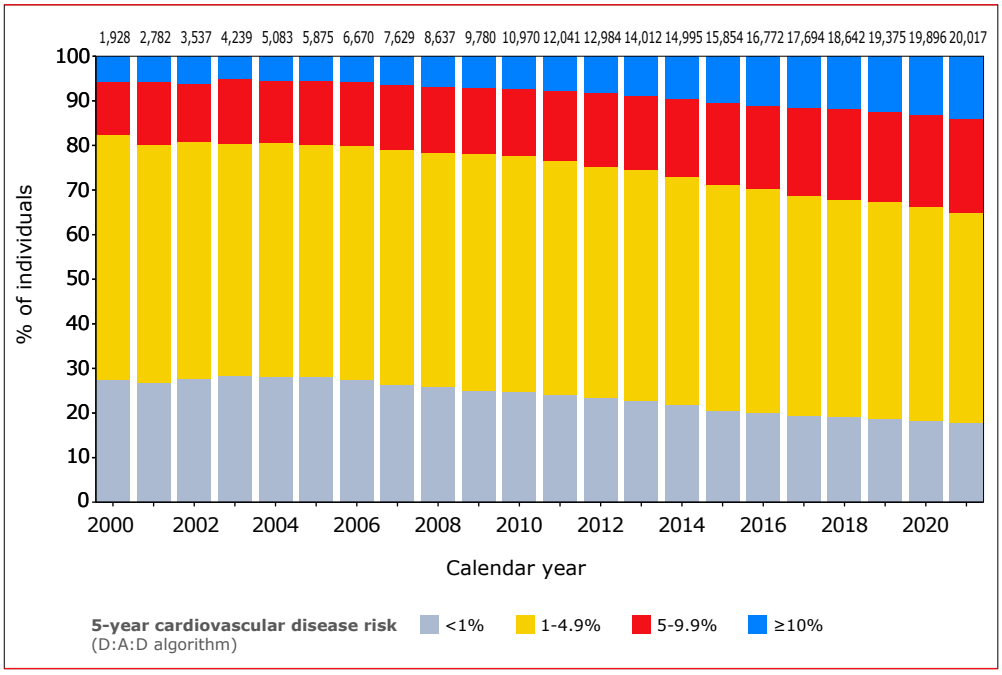
Legend: BMI = body mass index.

Figure 3.6: *Distribution of graded blood pressure at the end of each calendar year in (A) individuals known to be receiving antihypertensive treatment, and (B) those individuals not recorded as being treated for hypertension. For each individual, the last available systolic and diastolic blood pressure measurement in each year was selected. Blood pressure was graded according to the classification recommended in the guidelines for the management of arterial hypertension by the European Society of Hypertension and by the European Society of Cardiology[30]. Normal: systolic blood pressure (SBP) <130 mmHg or diastolic blood pressure (DBP) <85 mmHg; high normal: SBP 130–139 mmHg or DBP 85–89 mmHg; grade 1 hypertension SBP 140–159 mmHg or DBP 90–99 mmHg; grade 2 hypertension SBP 160–179 mmHg or DBP 100–109 mmHg; grade 3 hypertension SBP ≥ 180 mmHg or DBP ≥ 110 mmHg. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.*



Legend: *BP = blood pressure; HT = hypertension.*

Figure 3.7: Estimated five-year risk of coronary heart disease at the end of each calendar year according to the algorithm from the D:A:D: study[28]. Calculation of risk included variables such as total cholesterol, HDL cholesterol, and systolic blood pressure. Values for these variables were estimated on the basis of a 'last observation carried forward' approach. An accurate assessment of an individual's risk requires recent measurements of lipid levels and blood pressure. Recent HDL cholesterol measurements were often lacking or absent. Risk could not be estimated in younger individuals, in particular, because of missing data. Hence, the reported absolute number of individuals is smaller than the number of individuals in active follow up at the end of each calendar year, and older individuals are over-represented. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.



Use of preventive therapy for myocardial infarction or stroke

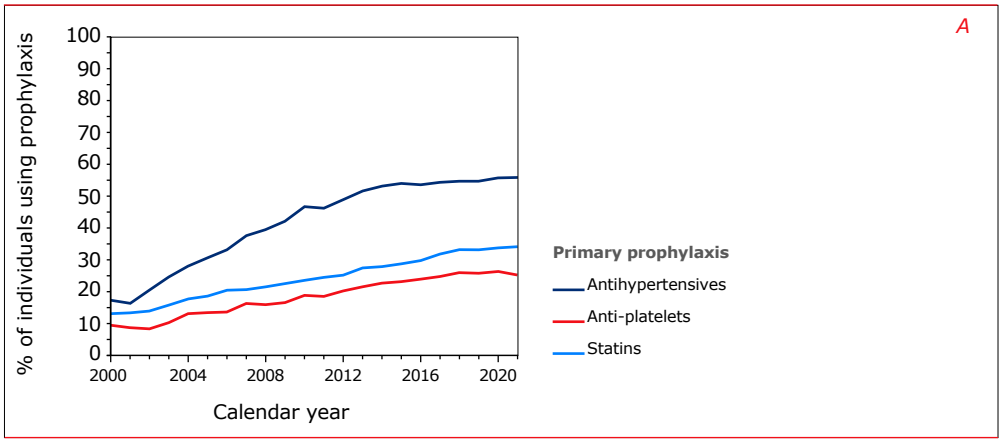
Primary prevention

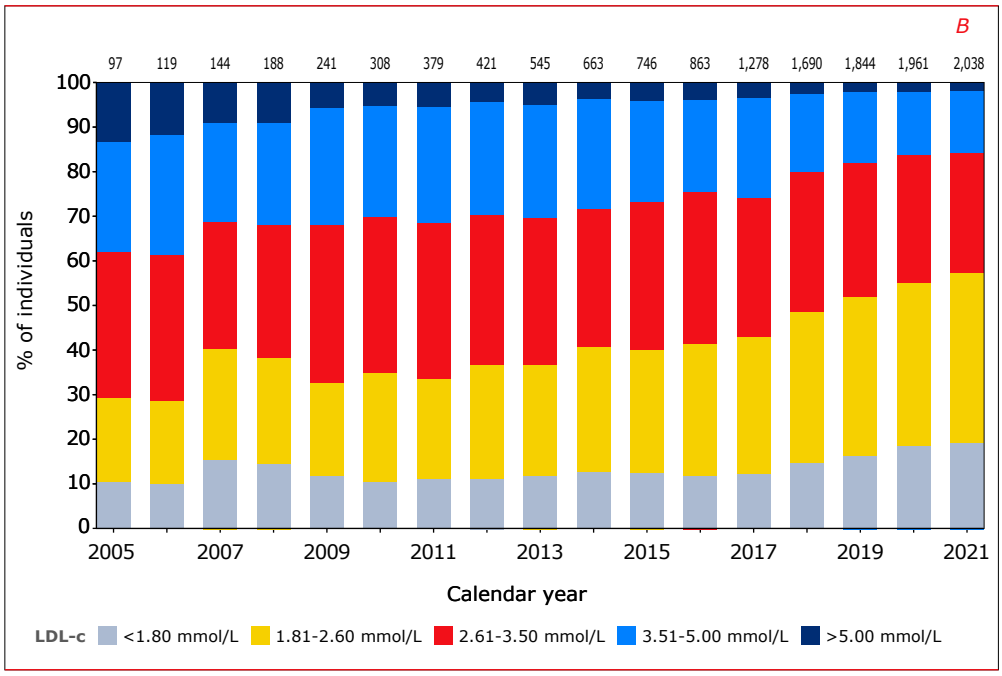
According to EACS guidelines, statin therapy should be offered to individuals with type 2 diabetes or a ten-year CVD risk ≥10%. They also recommend that angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers (CCB), (thiazide) diuretics, and non-dihydropyridine CCB (verapamil or diltiazem) should be offered to individuals with a systolic blood pressure ≥140 mmHg or diastolic blood pressure fff90 mmHg and a ten-year CVD risk ≥20%. For individuals aged 50 years and over with a ten-year CVD risk ≥20%, acetylsalicylic acid is recommended[31]. In general, the Dutch cardiovascular risk management (CVRM) guidelines closely resemble the EACS guidelines, with the

notable exception that the Dutch guidelines do not recommend the use of acetylsalicylic acid in older people with increased CVD risk, but without prior clinical CVD[32]. *Figure 3.8A* shows trends in the use of these medications in individuals without a prior stroke, myocardial infarction, or cardiovascular surgical procedure.

The percentage of individuals for whom primary prevention with statins and the above-mentioned antihypertensive drugs (referred to collectively hereafter as antihypertensives) is recommended, has increased over time, although the curve for antihypertensives has levelled off somewhat since 2013. Even though the percentage of individuals who were at high risk (aged 50 years and over, who used acetylsalicylic acid/clopidogrel as primary prevention) increased slowly prior to 2014, the overall proportion remained minimal and has remained stable during the last few years. Only about half of the individuals who received treatment with antihypertensive drugs or statins for the primary prophylaxis of myocardial infarction or stroke reached treatment targets (below 2.6 mmol/l). *Figure 3.6A* shows that of all individuals using antihypertensive drugs, only about half had a normal blood pressure in recent years. *Figure 3.8B* shows the distribution of LDL-cholesterol in subjects who use statins for primary CVD prophylaxis. The proportion of individuals with an LDL-c below 1.8 mmol/l or between 1.8 and 2.6 mmol/l was 10.3% and 18.6% respectively, in 2005. These increased to 19.2% and 38.0% respectively, in 2021.

Figure 3.8: (A) Percentage of individuals without a previous myocardial infarction, stroke, or cardiovascular surgical procedure who, according to European AIDS Clinical Society (EACS) guidelines, should be offered statin therapy, antiplatelet therapy, or antihypertensives for primary prevention of myocardial infarction or stroke. (B) Distribution of LDL-cholesterol in individuals using statins for primary prevention of myocardial infarction or stroke.

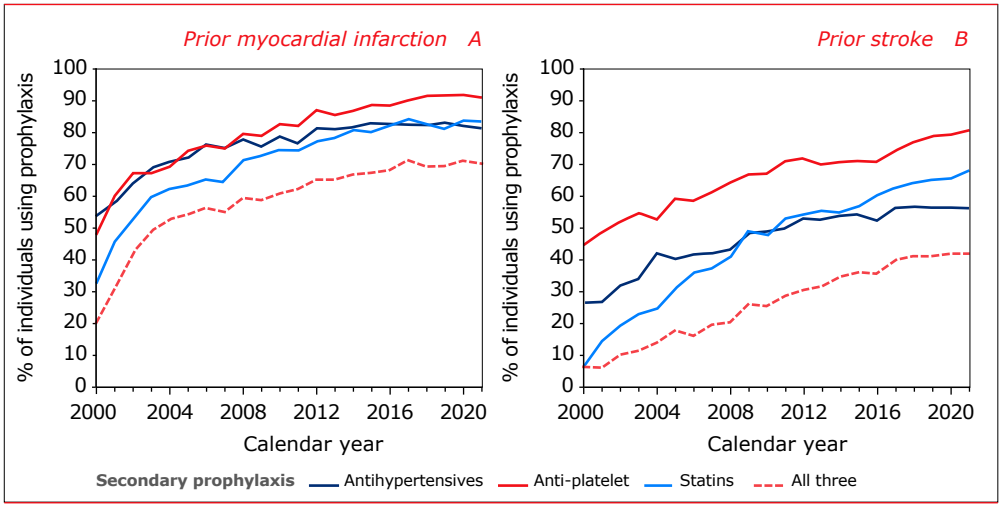




Secondary prophylaxis for myocardial infarction or stroke

According to all guidelines, individuals with a prior myocardial infarction or ischaemic stroke should receive lifelong treatment with statins, antihypertensives (ACE inhibitors, beta blockers or angiotensin receptor blockers), as well as low-dose acetylsalicylic acid/clopidogrel[33,34]. *Figure 3.9A* shows that the percentages of individuals using statins, acetylsalicylic acid/clopidogrel or antihypertensives after a myocardial infarction, increased between 2000 and 2021: in 2021, 83.5% of individuals with a prior myocardial infarction used statins, 81.5% used antihypertensives, and 91.1% used acetylsalicylic acid/clopidogrel. Although the use of statins and antihypertensives after an ischaemic stroke also increased over time, in 2021 these medications were used less frequently after a stroke than after a myocardial infarction (68.3% used statins, 56.4% used antihypertensives, and 80.8% used acetylsalicylic acid/clopidogrel) (*Figure 3.9B*).

Figure 3.9: *Percentage of individuals with (A) myocardial infarction or (B) ischaemic stroke using statin therapy, antiplatelet therapy, or antihypertensives.*



Chronic kidney disease

Glomerular filtration rate (GFR) is a marker of renal function and is commonly estimated by one of three formulae, namely the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD), or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations[35]. As all three equations used to estimate GFR (eGFR) are based on serum creatinine, they may be markedly affected by rapid changes in muscle mass, as is seen in some individuals with advanced HIV disease who commence ART. Of these equations, both the Cockcroft-Gault and the CKD-EPI equations have been validated in individuals with HIV[35,36]. However, because the CKD-EPI equation is the one most often used in clinical practice, we have chosen to report eGFR values as estimated by this equation. The distribution of eGFR categories in ml/min/1.73m^2 (90 or above, normal kidney function; 60-89, mildly reduced; 30-59, moderately reduced; 15-29, severely reduced; and below 15, very severely reduced kidney function) is shown in *Figures 3.10A* and *3.10B* for men and women. The percentage of men with normal kidney function decreased over time from 74.5% in 2007, to 44.9% in 2020, and this pattern was similar in women. Typically, eGFR decreases with increased age, as shown in *Figure 3.11*, 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

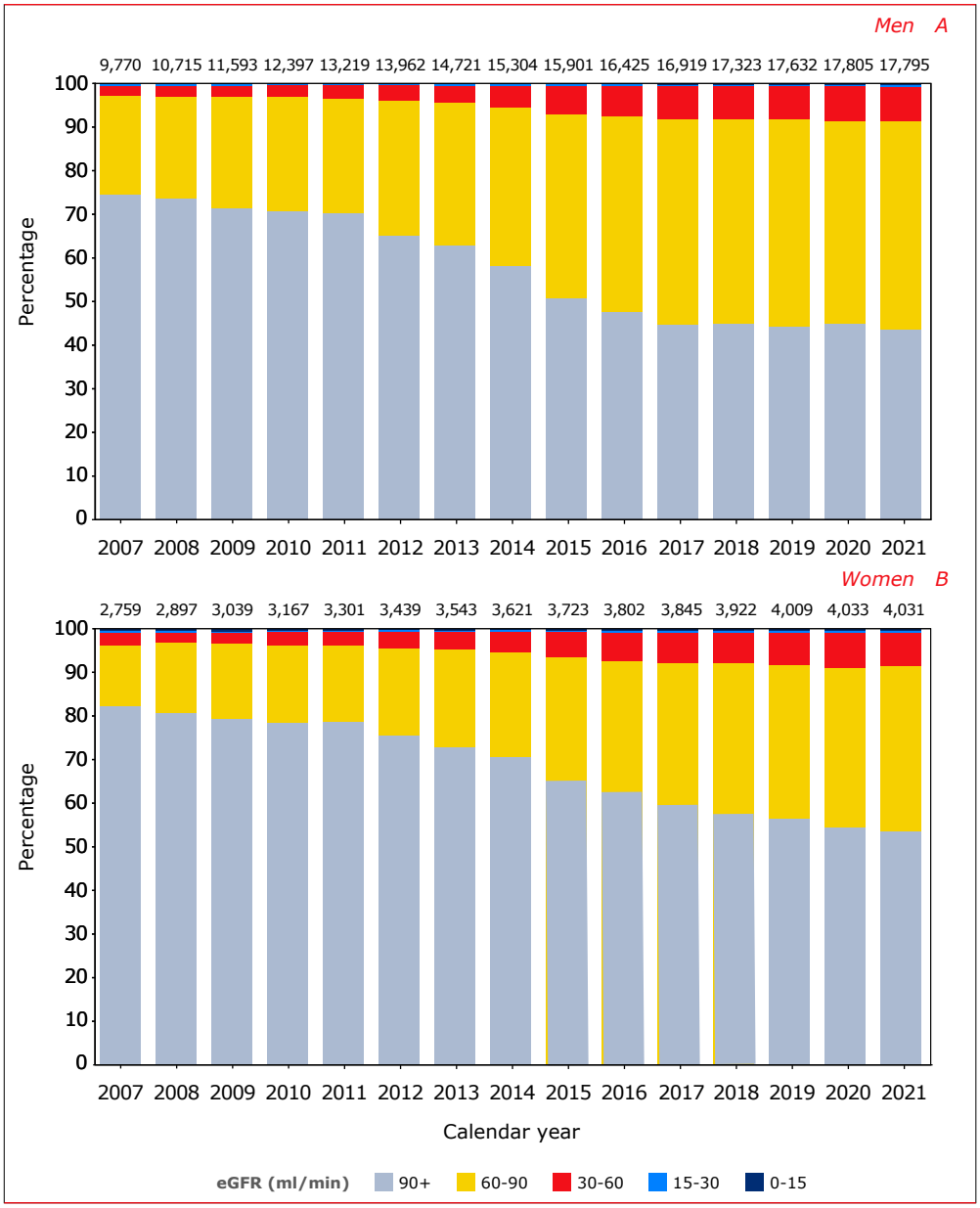
In individuals with an eGFR above 60ml/min/1.73m^2 at the time of inclusion in the analyses, who did not have a previously confirmed CKD, the crude incidence of CKD (defined as eGFR below 60ml/min/1.73m^2 confirmed by a second test at least 26 weeks later) varied over time (*Figure 3.4C*). Routine collection 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 2015-20. 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 2016-21 completely disappeared (even reversed) in comparison to 2008-10 and 2011-15. This strongly suggests that the increase in CKD seen in recent years is largely due to increases in serum creatinine caused by ARV-induced reversible inhibition of two transporters that mediate tubular secretion of creatinine, without affecting the true glomerular filtration rate (namely, organic cation transporter 2 [OCT2], and multidrug and toxin extrusion transporter [MATE1]) and is therefore not a true increase in CKD.

Figure 3.10: *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.*



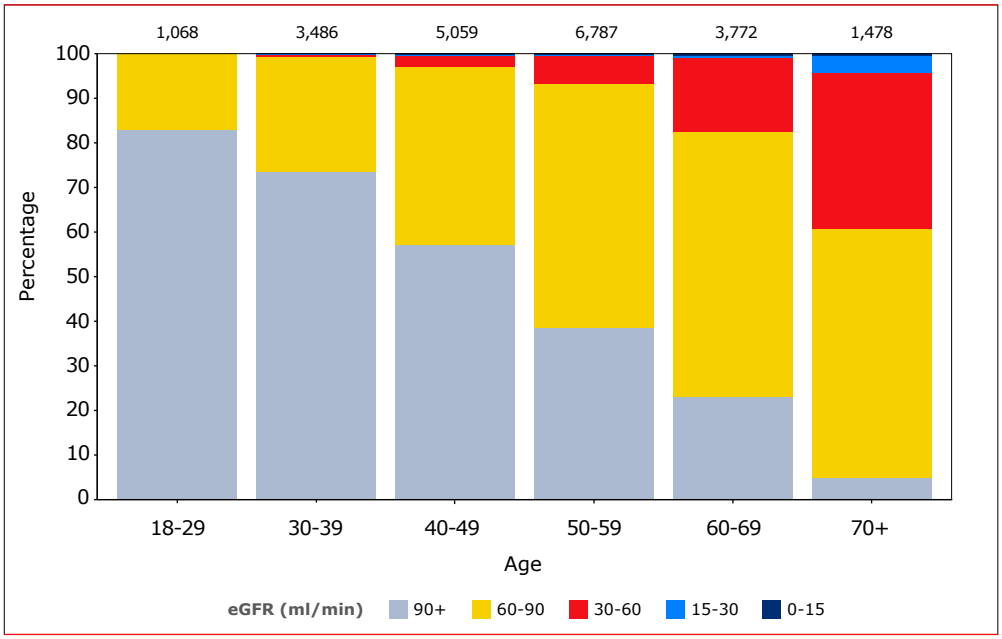
Legend: *eGFR = estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60–89 ml/min/1.73m²: mildly reduced; 30–59 ml/min/1.73m²: moderately reduced; 15–29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

Table 3.6: Crude chronic kidney disease incidence per 1,000 person years of follow up in 2008–14 and 2015–21, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)
2008–2014	7.1 (6.3–7.9)	0.78 (0.70–0.87)	7.4 (5.9–9.2)	0.90 (0.70–1.09)
2015–2021	11.6 (10.8–12.4)	1 (reference)	12.4 (10.7–14.3)	1 (reference)

**Standardised according to the observed age distribution in 2015–21.*
***Legend:** CI = confidence interval; PYFU = person years.*

Figure 3.11: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2021 for different age categories. For each individual, the last available measurement in 2021 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 2021, 2,108 diagnoses of non-AIDS-defining malignancies in 1,944 unique individuals were recorded in SHM's database. An additional 845 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 (16.4%);
- haematological malignancies (excluding AIDS-defining non-Hodgkin's lymphoma, 13.7%);
- intestinal cancer (mainly oesophageal, gastric, intestinal, and rectal cancers, but excluding liver cancer, 13.4%);
- invasive anal cancer (not AIN, 11.7%);
- prostate cancer (9.8%); and
- head and neck cancers (8.3%).

Figure 3.12 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: 3.13*, 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 3.4D*. The age-standardised incidence in men was statistically significantly lower in the period 2016-21, compared to 2000-10, and borderline significantly lower compared to 2011-15 (*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:

- older age group;
- acquiring HIV-1 through injecting drugs or contact with blood or blood products;
- lower current CD4 cell count (CD4 below 350 cells/mm^3);
- low body mass index;
- prior AIDS;
- chronic HBV co-infection; and
- current or past smoking (*Appendix Table 3.5*).

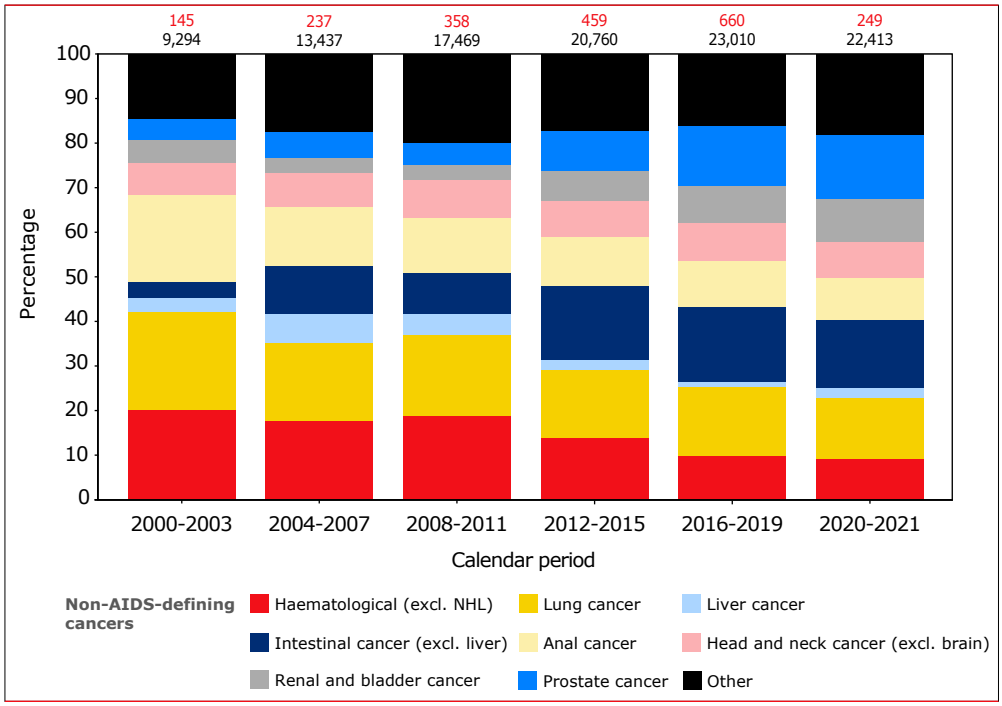
Furthermore, people who had been pre-treated with mono or dual-NRTI-based regimes prior to starting ART had an independently increased risk for NADM, compared with those who were therapy-naïve prior to starting ART (relative risk [RR] 1.18, 95% CI 1.02-1.36). Of note, independent of all other risk factors investigated, people who initiated ART within 12 months of their last negative HIV test had a significantly lower risk for NADM (RR 0.57, 95% CI 0.39-0.83) 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 2021, the overall five-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 50.0%, compared with 73.4% for CVD, 83.2% for DM, and 86.2% for CKD (*Appendix Figure 3.1*). In the same period, the five-year survival rate of all adults newly entering care in one of the Dutch HIV treatment centres was 95.7%, and 82.2% for those newly entering care with an AIDS diagnosis. The five-year survival rates following the most common non-AIDS-defining malignancies are shown in *Table 3.7* and *Appendix Figure 3.2*.

Anal cancer

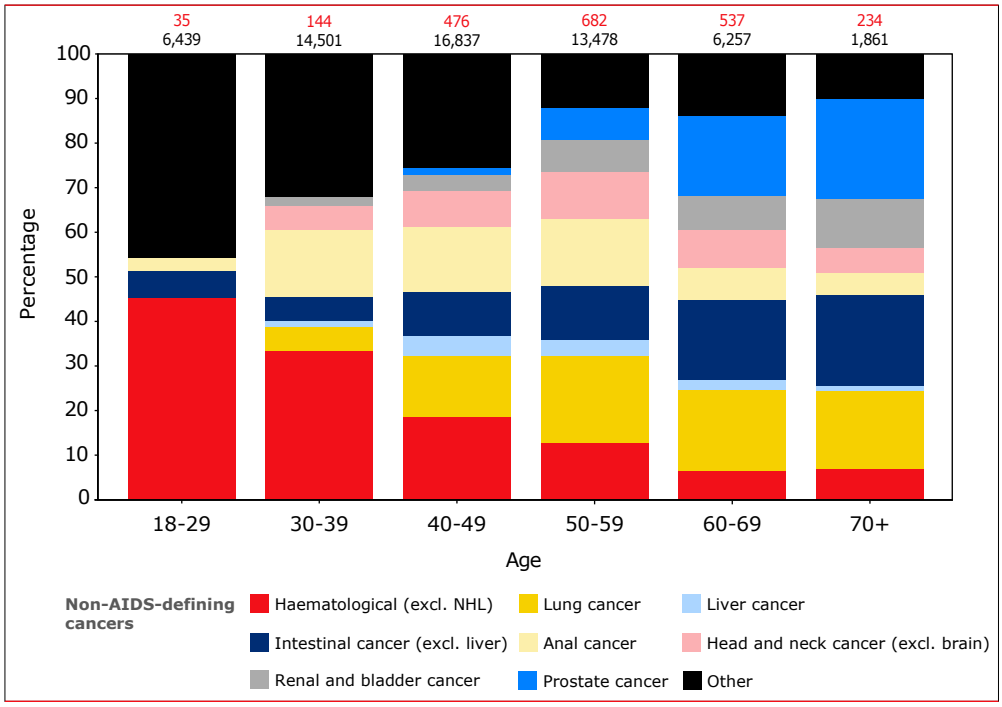
In total, 236 men with HIV and 11 women with HIV were diagnosed with anal cancer. Among men with HIV, the incidence of anal cancer fluctuated between 0.4 and 1.5 cases per 1,000 PYFU between 2000 and 2021 (*Figure 3.4G*). A 2015 study exploring the incidence of anal cancer among PWH in the Netherlands showed a significantly higher incidence of anal cancer in men who have sex with men (MSM), than in heterosexual men[37]. However, in this chapter, we will not report on the trend in anal cancer among heterosexual men over time, as the number of heterosexual men with anal cancer is too small (n = 25) to analyse.

Figure 3.12: Relative changes in non-AIDS-defining malignancies between 2000 and 2021 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 3.13: 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 2021.



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

Table 3.7: Most common non-AIDS-defining malignancies diagnosed in 2000-21, excluding non-melanoma skin cancer and pre-malignant lesions found by cervical and anal screening.

non-AIDS malignancy	# of malignancies	%	Five-year survival (%)
Lung cancer	345	16.4	15.3
Hematological (excl. NHL)	289	13.7	64.4
Intestinal cancer (excl. liver)	283	13.4	32.8
Anal cancer	247	11.7	66.3
Prostate cancer	206	9.8	80.1
Head and neck cancer (excl. brain)	174	8.3	57.3
Renal and bladder cancer	139	6.6	62.8
Other cancers	117	5.6	45.3
Malignant melanoma	91	4.3	73.6
Liver cancer	64	3.0	16.8
Breast cancer	57	2.7	79.1
Testicular cancer	39	1.9	88.4
Gynecological cancer (excl. cervical)	33	1.6	71.8
CNS cancer	24	1.1	54.9

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 2000-10, 2011-15, and 2016-21, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)	Incidence/1000PY (95%CI)	Standardised Inc. Ratio (95%CI)
2000-2010	6.6 (6.0-7.1)	1.31 (1.20-1.42)	3.2 (2.5-4.0)	1.13 (0.88-1.39)
2011-2015	6.6 (6.0-7.2)	1.02 (0.93-1.11)	4.4 (3.4-5.5)	1.06 (0.82-1.31)
2016-2021	8.0 (7.5-8.6)	1 (reference)	5.2 (4.3-6.3)	1 (reference)

**Standardised according to the observed age distribution in 2011-21.*

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

Multimorbidity

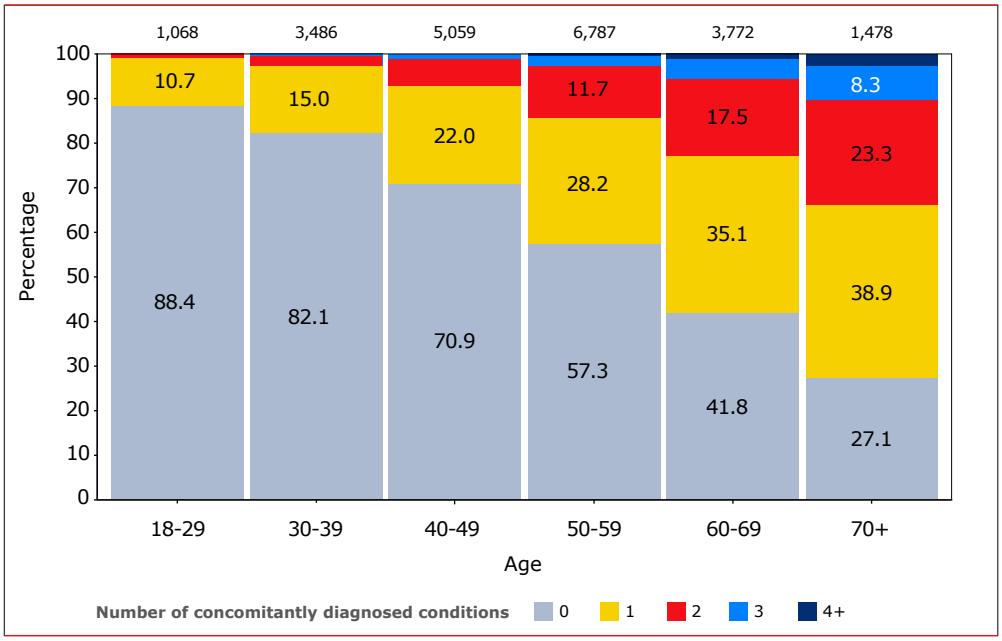
We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infections and AIDS diagnoses did not contribute to the multimorbidity count. The following comorbidities and conditions were taken into account:

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 3.4 shows the prevalence of each individual comorbidity over calendar time. *Figure 3.14* shows the distribution of the number of concomitantly-diagnosed conditions in various age categories of the adult population in 2021. The number of concomitant conditions was slightly higher in women than in men for all age categories (*Appendix Figure 3.3*). Moreover, although the average number of concomitant conditions has steadily increased over the past ten years due to the increasing average age of the cohort, the prevalence of multimorbidity by age category has remained stable over the same period (*Appendix Figure 3.5*). After adjusting for the variables listed in *Appendix Table 3.2*, multimorbidity was independently associated with increased risk of mortality (RR 2.15, 95% CI 2.07-2.23, $p<0.001$, per additional comorbidity diagnosed).

Figure 3.14: Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2021. 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[aa]) 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 2021, our count revealed:

- 19.8% of adults in active follow up had no recorded comedication use
- 29.5% used one comedication;
- 16.2% used two comedications;
- 10.7% used three comedications; and
- 7.3% used four comedications.

A further 16.5% 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 3.15*): 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 3.16A*) and those with more comorbidities (*Figure 3.17*) 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 3.16B*). Finally, in adults receiving ART in the period 2007-21, polypharmacy was also associated with an increased risk of death (RR 2.23, 95% CI 2.01-2.47, $p<0.001$) 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 2021 are listed in *Table 3.9*.

Table 3.9: Use of comedications in 2021.

Comedication use in 2021	N	%
ATC group		
Vitamins	6184	12.0
Lipid modifying drugs	4360	8.5
Drugs for acid related disorders	3767	7.3
Drugs acting on the renin-angiotensin system	3247	6.3
Psycholeptics drugs (antipsychotics, anxiolytics, hypnotics, sedatives)	3089	6.0
Antithrombotic drugs	2711	5.3
Drugs for obstructive airway diseases	2437	4.7
Psychoanaleptics (antidepressants, psychostimulants)	2239	4.4
Drugs used in diabetes	2066	4.0
Mineral supplements	2056	4.0
Urological drugs	1694	3.3
Beta blocking drugs	1650	3.2
Calcium channel blockers	1484	2.9
Antianaemic drugs	1127	2.2
Diuretic drugs	1122	2.2
Antibacterial drugs	1102	2.1
Sex hormones and modulators of the genital system	1080	2.1
Corticosteroids systemic	918	1.8
Analgesic drugs	870	1.7
Antiepileptic drugs	791	1.5
Antiviral drugs	726	1.4
Cardiac therapy	696	1.4
Nasal preparations	643	1.3
Topical dermatological corticosteroids	640	1.2
Antidiarrheals, intestinal anti-inflammatory/anti-infective drugs	472	0.9
Antimycotic drugs	457	0.9
Drugs affecting bone structure and mineralisation	446	0.9
Thyroid therapy	359	0.7

Figure 3.15: 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.

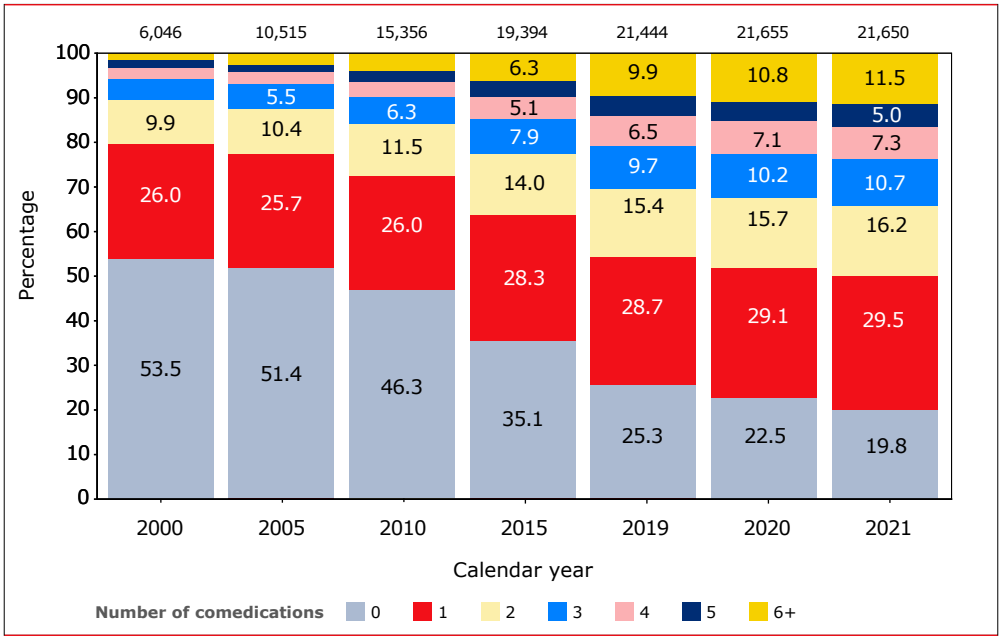
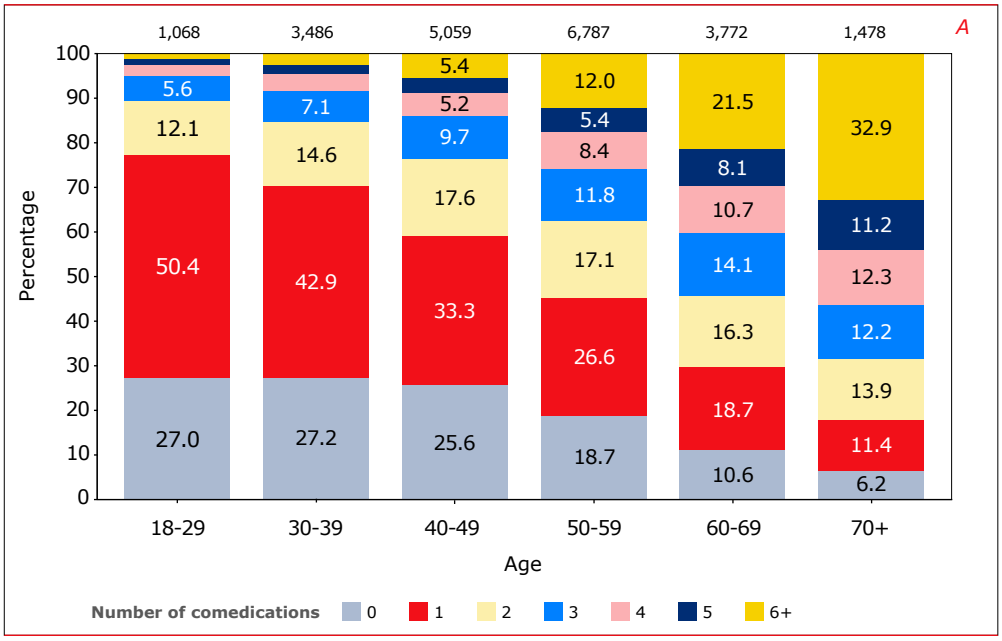


Figure 3.16: Number of comedications used by (A) age group, and (B) gender in 2021. The numbers at the top of each bar represent the number of individuals contributing data to that age/gender category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



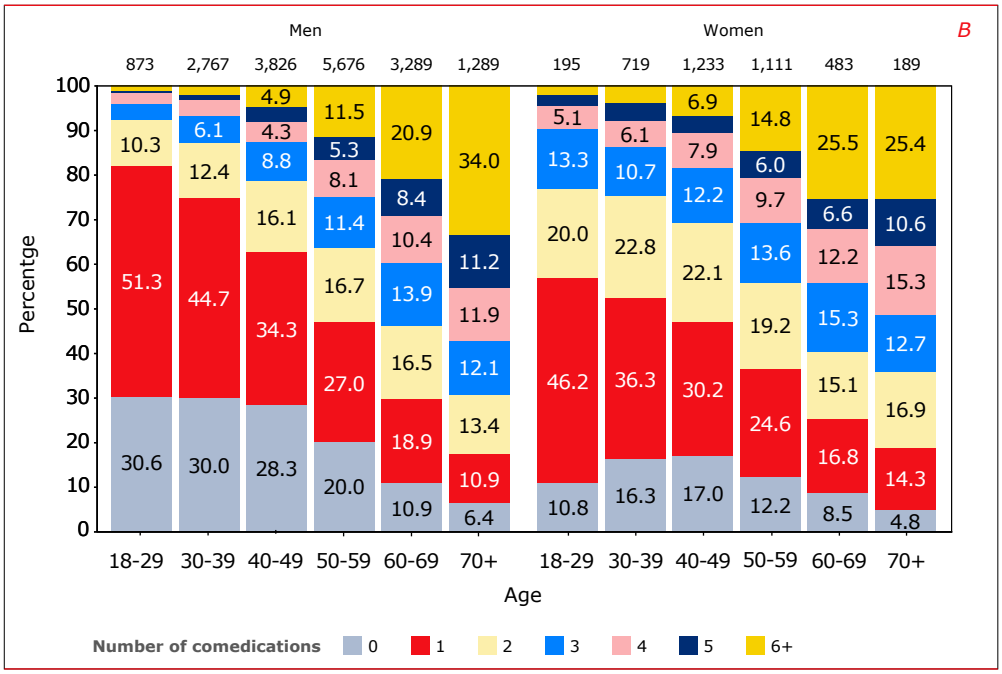
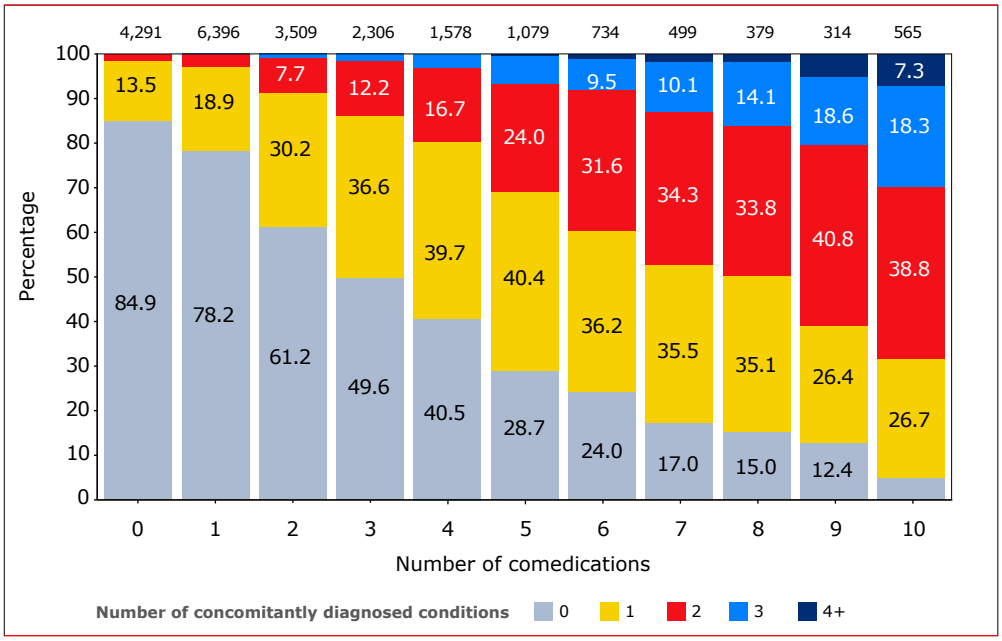


Figure 3.17: Number of comedications used in relation to the number of prevalent comorbidities. The numbers at the top of each bar represent the number of individuals contributing data to that category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per category.



Summary and conclusions

AIDS, mortality and causes of death

AIDS-related deaths have decreased dramatically since 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 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[38,39].

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 8.51 deaths per 1000 person years in 2019, to 9.30 in 2020 and 11.24 in 2021. The increase in 2020 and 2021 is 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[b].

Diabetes and cardiovascular disease

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

Cardiovascular risk factors

The proportion of adults with HIV at high (5-10%), or very high (more than 10%) cardiovascular risk slowly increased from 12.0% and 5.8% respectively in 2000, to 21.3% and 14.1% respectively in 2021. This increase largely reflects the increased average age of the population. We observed that cardiovascular risk management has improved over time, as illustrated by the increasing use of statins and antihypertensives, and the shift away from the use of antiretrovirals that have been demonstrated to be associated with increased cardiovascular risk, particularly

b Report "Sterfte en oversterfte in 2020 en 2021. Onderzoek door het CBS en het RIVM, in het kader van het ZonMw onderzoeksprogramma Oversterfte.", published by CBS and RIVM on 23 June 2022, accessed online at https://www.cbs.nl/nl-nl/longread/rapportages/2022/sterfte-en-oversterfte-in-2020-en-2021 [in Dutch].

in individuals with high underlying risk[45] (*Chapter 2*). Significant room for further improvement remains, however, particularly given the suboptimal use of statin therapy, antihypertensive therapy, and low-dose acetylsalicylic acid as secondary prevention following a myocardial infarction or ischaemic stroke, and the low, albeit slowly improving, uptake of these medications in the prevention of primary cardiovascular disease. The increased availability of preferred antiretroviral therapy options that do not contain pharmacological boosters that can interfere with these preventive medicines, has made it easier to implement proper cardiovascular risk management.

The clinical significance of the increase in BMI over time, especially in women, requires further study. Recent results suggest that weight gain after starting ART is associated with lower mortality for normal-weight individuals, but they show no clear benefit for overweight or obese individuals[46]. However, another study found that weight gain after starting 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[47]. Prospective longitudinal monitoring of lipid levels, smoking status, blood pressure, weight and other risk factors will be important to further optimise the assessment of cardiovascular risk in our increasingly ageing 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[48,49], and the use of tenofovir disoproxil

fumarate, atazanavir/ritonavir and lopinavir/ritonavir, to be additional independent predictors of chronic renal impairment[50]. Moreover, renal impairment in the population with HIV is associated with an increased risk of cardiovascular disease[51]. The increase in CKD in our population appears to be largely caused by the increased use of dolutegravir, bictegravir, rilpivirine, and cobicistat, all of which cause reversible inhibition of tubular excretion of creatinine, without causing a true decrease in glomerular filtration.

Non-AIDS-defining malignancies

The most common non-AIDS-defining malignancies (NADM) in the Netherlands are lung, intestinal, anal, and head and neck cancer, as well as Hodgkin's lymphoma. The crude incidence of NADM has remained stable over time, and we also observed a decline in age-standardised incidence of NADM in men, and to a lesser extent in women. In addition, our analyses showed that individuals diagnosed with NADM a more likely to be older. This is in line with data from other cohorts, including the Swiss HIV cohort[49-52]. Additional risk factors for NADM identified in our analyses were: current or past smoking; a CD4 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[56]. Importantly, individuals who had initiated ART earlier in infection (i.e. within 12 months of a last negative HIV test), had a significantly lower risk of NADM (RR 0.57, 95% CI 0.39-0.83, p = 0.004), independent of other traditional and HIV-related risk factors. The five-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 50.0%.

Multimorbidity and polypharmacy

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

Polypharmacy, defined as the concomitant use of five or more medications in addition to ART, is becoming more prevalent, mainly because of the increased age of the cohort and the associated rise in the prevalence of age-associated, non-AIDS comorbidities. In 2000, 3.3% of adults used five or more non-antiretroviral comedications alongside their ART regimen, and this steadily increased to 16.5% of adults in active follow up in 2021. 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 2007-21, polypharmacy was also strongly and independently associated with an increased risk of death, independent of demographic and HIV-related parameters, chronic HBV and HCV co-infections, smoking status, and number of comorbidities.

Recommendations

The proportion of individuals dying of AIDS in the Netherlands has markedly declined throughout the ART era, but in order to reach the goal of zero AIDS-deaths by 2022, 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 such as the ongoing Comorbidity and Aging with HIV (AGEhIV) cohort study have provided further insights into the independent contribution of HIV and HIV-associated factors, such as innate and adaptive immune and coagulation activation, and inflammation. This will hopefully guide the development of interventions that target relevant pathophysiological mechanisms[9,60].

It is important to note that the risk of many, if not each, of the comorbidities frequently identified in people 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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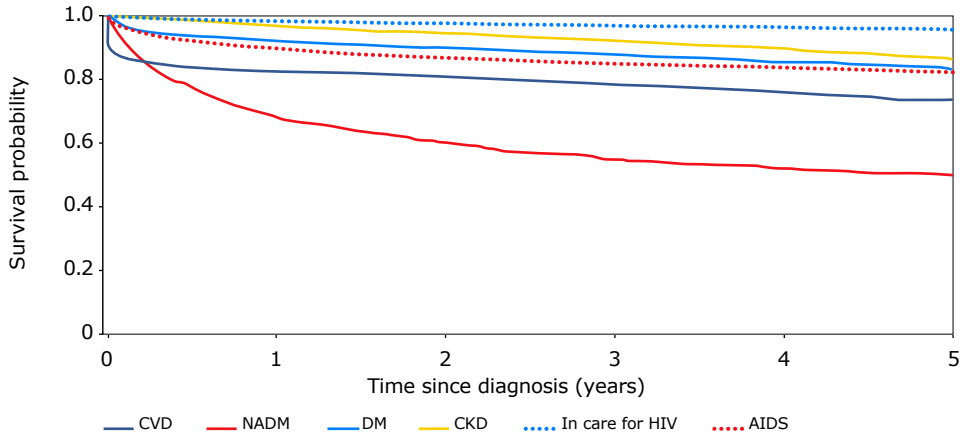
Appendix: supplementary figures and tables

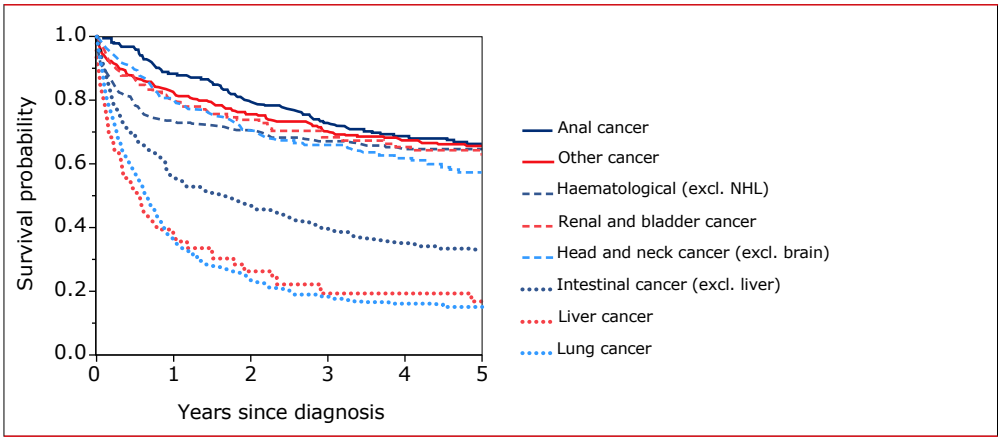
Appendix Figure 3.1: *Estimated five-year survival following the diagnosis of cardiovascular disease, non-AIDS-defining malignancy, diabetes mellitus, and chronic kidney disease. Two reference groups are included: survival from date of entry into HIV care (after 1 January 2000), and from date of first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



Time since diagnosis (years)	0	1	2	3	4	5
CVD	1,757	1,376	1,224	1,084	954	819
NADM	1,639	1,063	845	695	581	491
DM	1,624	1,391	1,232	1,116	985	876
CKD	2,543	2,205	1,977	1,739	1,458	1,148
In care for HIV	23,134	21,233	20,081	18,898	17,732	16,560
AIDS	3,738	3,190	2,962	2,773	2,613	2,446

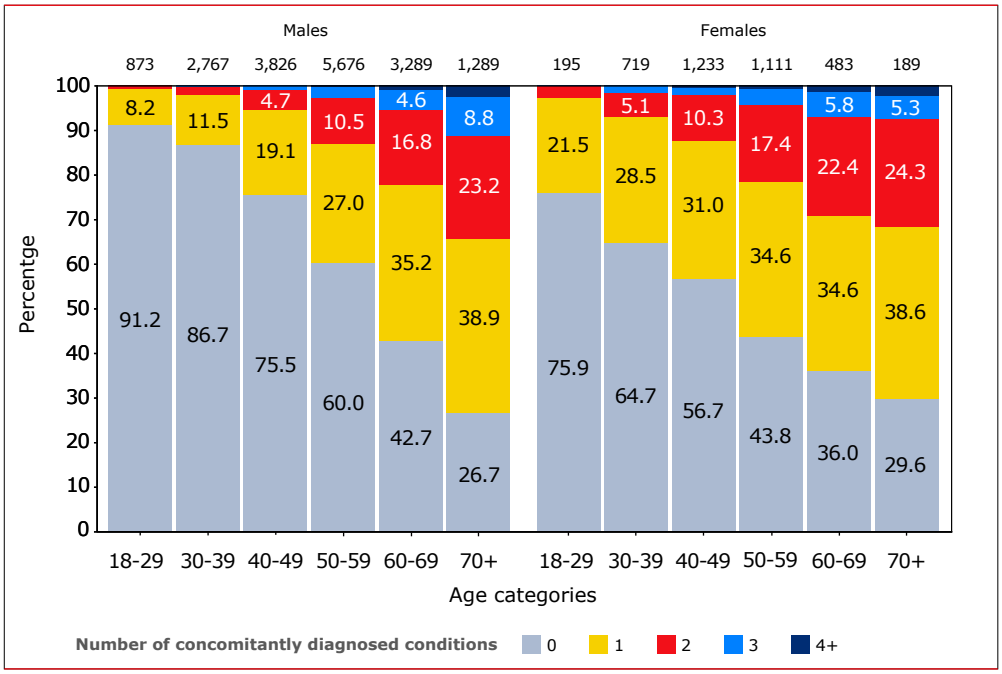
Legend: *KM = Kaplan-Meier; CVD = cardiovascular disease; NADM = non-AIDS defining malignancy; DM = diabetes mellitus; CKD = chronic kidney disease.*

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

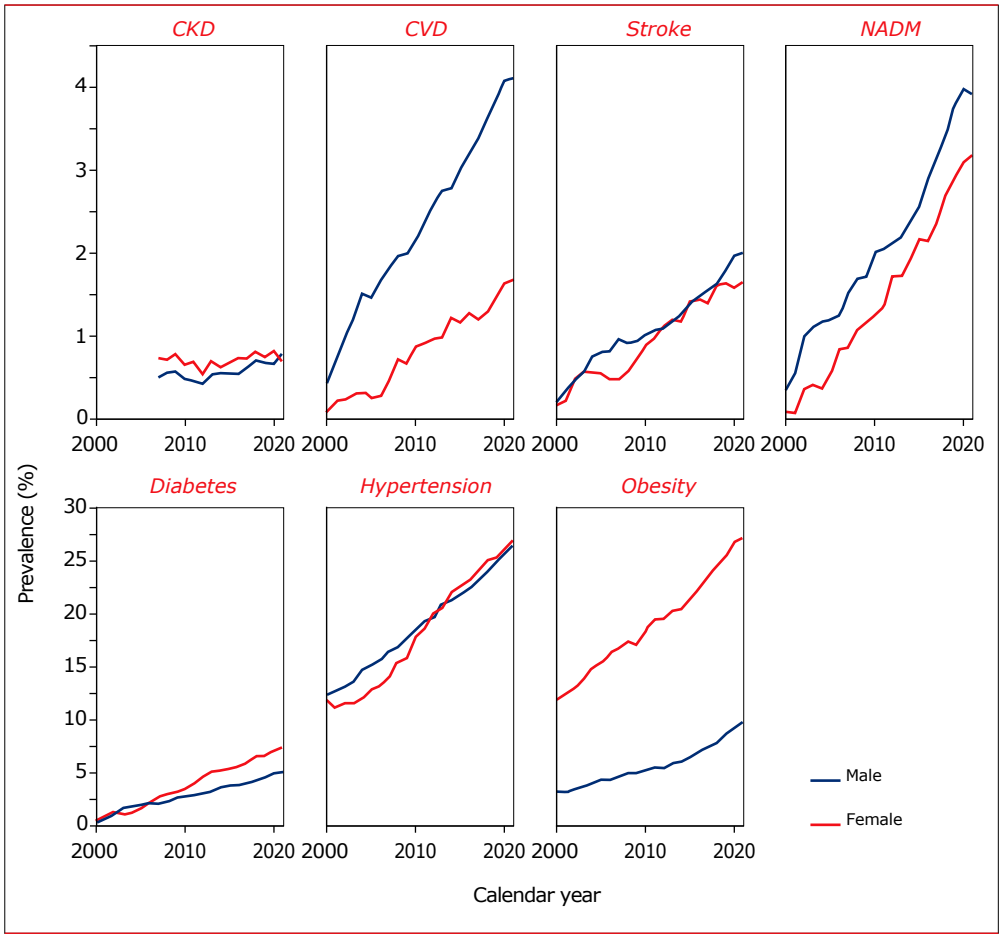


Legend: *KM = Kaplan-Meier; excl. = excluding; NHL = non-Hodgkin's lymphoma.*

Appendix Figure 3.3: *Prevalence of non-AIDS multimorbidity by gender in the adult population in 2021. The numbers at the top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.*

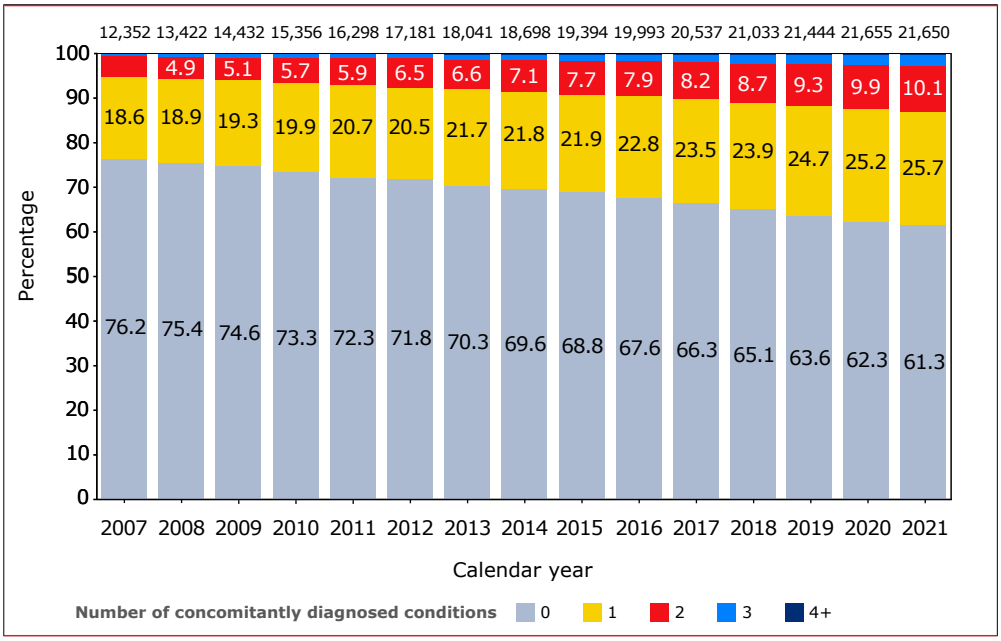


Appendix Figure 3.4: *Prevalence of non-AIDS comorbidities in the adult population between 2000 and 2021.*



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

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



Appendix Table 3.1: *Absolute number of causes of death among PWH during the periods 1996–2000, 2001–05, 2006–10, and 2011–21.*

	Calendar period										
Causes of death	**96–00**	**01–05**	**06–10**	**11–15**	**16–21**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
1. AIDS											
1.1 AIDS – infection	69	120	148	103	27	6	4	4	7	5	1
1.2 AIDS – malignancy	60	63	61	43	56	8	13	10	11	6	8
1.3 AIDS – unclassifiable	89	63	19	15	30	10	3	4	5	4	4
total	*218*	*246*	*228*	*161*	*113*	*24*	*20*	*18*	*23*	*15*	*13*
2. Non-AIDS malignancies	30	95	136	193	361	49	62	48	75	70	57
3. Cardiovascular disease											
3.1 Myocardial infarction	14	30	46	40	50	8	4	2	10	14	12
3.2 Stroke	3	11	13	11	23	7	3	3	2	3	5
3.3 Other CVD	6	24	26	50	76	16	10	16	10	11	13
total	*23*	*65*	*85*	*101*	*149*	*31*	*17*	*21*	*22*	*28*	*30*
4. Non-AIDS infection	23	42	32	27	66	7	3	10	7	16	23
5. Liver disease	15	28	55	43	27	6	7	8	.	2	4
6. Lung disease	7	11	30	38	69	13	14	9	16	7	10
7. Non-natural death											
7.1 Accident or violence	6	11	22	16	18	7	2	4	1	2	2
7.2 Suicide	12	30	30	52	59	10	12	11	5	14	7
7.3 Euthanasia	7	5	.	2	1	1	.	.	.	.	.
total	*25*	*46*	*52*	*70*	*78*	*18*	*14*	*15*	*6*	*16*	*9*
8. Alcohol and substance use	12	15	27	18	30	10	4	4	2	4	6
9. Other causes	21	24	23	43	86	13	8	18	10	14	23
10. Unknown	23	57	53	84	130	20	18	21	16	24	31
Total	**397**	**629**	**721**	**778**	**1,109**	**191**	**167**	**172**	**177**	**196**	**206**

Legend: *CVD = cardiovascular disease.*

Appendix Table 3.2: Adjusted risk factors for death and AIDS among PWH.

	Death			AIDS		
	RR (95%CI)	p-value	Overall p-value	RR (95%CI)	p-value	Overall p-value
Risk factors						
Male gender	1.24 (1.08-1.41)	0.002		0.99 (0.85-1.16)	0.900	
Region of birth						
Netherlands	1 (reference)		0.037	1 (reference)		0.112
Other	0.91 (0.83-0.99)	0.038		1.10 (0.98-1.23)	0.111	
HIV-1 transmission route						
Blood contact	0.85 (0.62-1.17)	0.317		0.81 (0.56-1.17)	0.261	
Heterosexual	1.08 (0.96-1.21)	0.188		0.92 (0.79-1.06)	0.257	
IDU	1.62 (1.36-1.94)	<.001		0.71 (0.55-0.92)	0.010	
MSM	1 (reference)		<.001	1 (reference)		0.031
Age *						
18-29	0.90 (0.66-1.24)	0.533	<.001	1.10 (0.89-1.35)	0.381	<.001
30-39	1 (reference)			1 (reference)		
40-49	1.53 (1.32-1.78)	<.001		1.09 (0.96-1.24)	0.206	
50-59	2.71 (2.34-3.14)	<.001		1.30 (1.13-1.50)	<.001	
60-69	4.90 (4.19-5.74)	<.001		1.37 (1.14-1.65)	<.001	
70+	11.58 (9.72-13.81)	<.001		2.01 (1.49-2.70)	<.001	
CD4 cell count **						
0-50	11.81 (9.88-14.12)	<.001	<.001	6.77 (5.46-8.39)	<.001	<.001
050-199	4.69 (4.11-5.34)	<.001		2.76 (2.35-3.25)	<.001	
200-349	1.98 (1.74-2.25)	<.001		1.53 (1.31-1.79)	<.001	
350-499	1.34 (1.18-1.53)	<.001		1.19 (1.01-1.39)	0.036	
500-749	1 (reference)			1 (reference)		
750+	0.86 (0.75-0.98)	0.027		1.04 (0.87-1.25)	0.662	
Per year longer on ART with HIV RNA>1000 cp/mL	1.06 (1.04-1.08)	<.001	<.001	1.04 (1.02-1.07)	0.002	0.002
Treatment status						
Treatment-experienced at start ART	0.95 (0.86-1.05)	0.290		0.64 (0.56-0.72)	<.001	
Treatment-naïve at start ART	1 (reference)			1 (reference)		
Prior AIDS event	1.71 (1.57-1.86)	<.001				

	Death			AIDS		
	RR (95%CI)	p-value	Overall p-value	RR (95%CI)	p-value	Overall p-value
Hepatitis B virus positive	1.27 (1.11–1.45)	<.001		1.10 (0.91–1.34)	0.308	
Hepatitis C virus positive	1.56 (1.36–1.79)	<.001		1.25 (1.04–1.50)	0.016	
Body mass index *						
0–18	3.07 (2.71–3.47)	<.001	<.001			
18–25	1 (reference)					
25–30	0.68 (0.61–0.75)	<.001				
30+	0.87 (0.75–1.02)	0.097				
Smoking status						
Current smoker	1.18 (1.04–1.33)	0.008	<.001	0.80 (0.71–0.90)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	2.00 (1.79–2.24)	<.001		0.99 (0.86–1.14)	0.859	
Early ART ***	0.88 (0.65–1.20)	0.425		1.26 (0.96–1.65)	0.093	

**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	48	2,741	17.5 (12.9–23.2)	3	159	18.9 (3.9–55.3)	8	161	49.8 (21.5–98.2)
050–199	198	10,305	19.2 (16.6–22.1)	11	842	13.1 (6.5–23.4)	38	1,034	36.7 (26.0–50.4)
200–349	411	22,830	18.0 (16.3–19.8)	16	1,052	15.2 (8.7–24.7)	83	2,062	40.3 (32.1–49.9)
350–499	528	45,789	11.5 (10.6–12.6)	36	1,788	20.1 (14.1–27.9)	120	3,640	33.0 (27.3–39.4)
500–749	772	99,502	7.8 (7.2–8.3)	58	5,063	11.5 (8.7–14.8)	198	8,099	24.4 (21.2–28.1)
750+	539	117025	4.6 (4.2–5.0)	42	6,047	6.9 (5.0–9.4)	170	10,447	16.3 (13.9–18.9)

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	1,832	2.2 (0.6–5.6)	27	491	54.9 (36.2–79.9)	6	99	60.5 (22.2–131.7)
	29	6,240	4.6 (3.1–6.7)	112	1,795	62.4 (51.4–75.1)	8	393	20.3 (8.8–40.1)
	78	14,382	5.4 (4.3–6.8)	208	4,491	46.3 (40.2–53.1)	26	844	30.8 (20.1–45.2)
	109	30,143	3.6 (3.0–4.4)	242	8,174	29.6 (26.0–33.6)	21	2,045	10.3 (6.4–15.7)
	233	67,274	3.5 (3.0–3.9)	262	14,891	17.6 (15.5–19.9)	21	4,175	5.0 (3.1–7.7)
	175	82,740	2.1 (1.8–2.5)	135	13,952	9.7 (8.1–11.5)	17	3,839	4.4 (2.6–7.1)

Appendix Table 3.4: *Absolute number of first AIDS events among PWH during the periods 1996–2000, 2001–05, 2006–10, 2011–15 and 2016–21.*

CDC event	1996–2000	2001–2005	2006–2010	2011–2015	2016–2019	2020–2021	Total	
	N	N	N	N	N	N	N	%
AIDS dementia complex – HIV encephalopathy	38	47	51	44	15	8	203	2.95
Bacterial pneumonia, recurring	48	64	67	78	76	21	354	5.15
CMV colitis/proctitis	1	.	1	2	3	.	7	0.10
CMV disease	27	34	29	33	3	.	126	1.83
CMV meningoencephalitis	.	.	.	.	1	.	1	0.01
CMV pneumonitis	.	.	.	.	9	9	18	0.26
CMV retinitis	31	20	12	12	10	.	85	1.24
Candidiasis oesophagitis	263	239	253	224	114	46	1139	16.57
Candidiasis lungs/bronchial/trachea	7	13	7	6	5	4	42	0.61
Cervical cancer, invasive	3	5	6	4	4	.	22	0.32
Coccidioidomycosis, extrapulmonary / disseminated	.	.	1	.	.	.	1	0.01
Cryptococcosis, extrapulmonary / disseminated	21	31	33	11	11	2	109	1.59
Cryptosporidiosis	22	12	11	12	2	1	60	0.87
Cystoisosporiasis	3	9	6	.	.	.	18	0.26
HIV wasting	48	56	77	77	52	17	327	4.76
HSV chronic ulcer	1	2	1	3	18	10	35	0.51
HSV oesophagitis	.	.	.	.	.	1	1	0.01
HSV pneumonitis	.	.	.	.	.	1	1	0.01
Herpes simplex virus	32	41	59	38	8	.	178	2.59
Histoplasmosis, extrapulmonary / disseminated	9	12	10	7	2	1	41	0.60
Kaposi sarcoma	154	153	188	139	77	24	735	10.69
Leishmaniasis visceral	.	1	2	2	2	.	7	0.10
Microsporidiosis	11	1	3	1	.	1	17	0.25
Mycobacterium avium/kansasii, extrapulmonary / disseminated	26	19	28	9	7	1	90	1.31
Mycobacterium avium/kansasii, pulmonary	1	2	.	1	8	2	14	0.20
Mycobacterium other / unspecified, extrapulmonary / disseminated	19	13	8	10	3	1	54	0.79
Mycobacterium other / unspecified, pulmonary	.	3	4	9	4	1	21	0.31
Non-Hodgkin's lymphoma (NHL)	57	87	80	96	55	23	398	5.79
Pneumocystis jirovecii extrapulmonary	1	1	3	.	1	.	6	0.09
Pneumocystis jirovecii pneumonia	333	300	326	265	164	59	1447	21.05
Primary CNS lymphoma	8	4	9	6	4	.	31	0.45

CDC event	1996–2000	2001–2005	2006–2010	2011–2015	2016–2019	2020–2021	Total	
	N	N	N	N	N	N	N	%
Progressive multifocal leukoencephalopathy	18	25	35	24	6	3	111	1.62
Salmonella sepsis, recurring	2	.	.	1	.	.	3	0.04
Talaromycosis	.	.	1	.	.	.	1	0.01
Toxoplasmosis of the brain	69	98	55	43	24	6	295	4.29
Tuberculosis, extrapulmonary / disseminated	79	113	80	54	19	11	356	5.18
Tuberculosis, pulmonary	105	174	118	74	44	4	519	7.55
Total	**1437**	**1579**	**1564**	**1285**	**751**	**257**	**6873**	**100.00**

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

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

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
Male gender	1.24 (1.11-1.37)	<.001	.	1.54 (1.26-1.88)	<.001	.
Region of birth						
Netherlands	1 (reference)	.	0.025	1 (reference)	.	0.731
Other	1.08 (1.01-1.16)	0.025	.	0.98 (0.86-1.11)	0.731	.
HIV-1 transmission route						
MSM	1 (reference)	.	<.001	1 (reference)	.	0.027
Heterosexual	1.20 (1.10-1.30)	<.001	.	1.19 (1.03-1.39)	0.021	.
IDU	1.31 (1.08-1.58)	0.005	.	1.40 (1.00-1.97)	0.048	.
Blood contact	1.21 (0.95-1.54)	0.114	.	1.06 (0.66-1.70)	0.806	.
Age *						
18-29	0.62 (0.47-0.81)	<.001	<.001	0.64 (0.32-1.26)	0.197	<.001
30-39	1 (reference)	.	.	1 (reference)	.	.
40-49	2.02 (1.79-2.29)	<.001	.	2.97 (2.20-4.02)	<.001	.
50-59	3.75 (3.31-4.24)	<.001	.	6.21 (4.62-8.34)	<.001	.
60-69	6.40 (5.60-7.31)	<.001	.	9.86 (7.27-13.39)	<.001	.
70+	10.21 (8.66-12.03)	<.001	.	16.41 (11.74-22.95)	<.001	.
CD4 cell count **						
0-50	3.94 (3.12-4.98)	<.001	<.001	3.24 (1.83-5.74)	<.001	<.001
050-199	1.79 (1.54-2.07)	<.001	.	1.70 (1.27-2.28)	<.001	.
200-349	1.25 (1.13-1.40)	<.001	.	1.40 (1.16-1.69)	<.001	.
350-499	1.04 (0.95-1.14)	0.392	.	1.00 (0.85-1.18)	0.984	.
500-749	1 (reference)	.	.	1 (reference)	.	.
750+	1.12 (1.03-1.22)	0.006	.	1.24 (1.08-1.42)	0.003	.
Per year longer with CD4<200 cells/mm^3	1.00 (0.98-1.02)	0.636	.	1.01 (0.98-1.04)	0.508	.
Prior AIDS event	1.21 (1.13-1.30)	<.001	.	1.17 (1.03-1.32)	0.013	.
Per year longer on ART while HIV RNA>1000 cp/mL	1.02 (1.00-1.04)	0.065	.	1.02 (0.98-1.05)	0.320	.
Treatment status						
Not (yet) started ART	1.17 (1.03-1.33)	0.019	<.001	1.33 (1.00-1.75)	0.047	0.032
Treatment-experienced at start ART	1.27 (1.16-1.39)	<.001	.	1.16 (0.98-1.37)	0.078	.
Treatment-naive at start	1 (reference)	.	.	1 (reference)	.	.
Per year longer on ART	1.01 (1.00-1.01)	0.054	.	1.00 (0.99-1.02)	0.477	.
Early ART within 12 months after last HIV-negat	0.81 (0.66-1.00)	0.051	.	1.18 (0.88-1.58)	0.268	.

Non-AIDS-defining malignancy			Diabetes mellitus			CKD		
IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value	IRR (95%CI)	p-value	Overall p-value
1.05 (0.88-1.25)	0.605	.	1.28 (1.09-1.49)	0.002	.	0.62 (0.54-0.72)	<.001	.
1 (reference)	.	0.006	1 (reference)	.	<.001	1 (reference)	.	<.001
0.85 (0.75-0.96)	0.007	.	1.53 (1.36-1.71)	<.001	.	0.76 (0.69-0.85)	<.001	.
1 (reference)	.	0.135	1 (reference)	.	<.001	1 (reference)	.	0.057
1.00 (0.87-1.16)	0.964	.	1.44 (1.25-1.66)	<.001	.	0.99 (0.87-1.13)	0.899	.
1.33 (1.00-1.77)	0.053	.	1.50 (1.08-2.08)	0.015	.	1.43 (1.09-1.87)	0.010	.
1.43 (1.00-2.03)	0.049	.	1.53 (1.06-2.19)	0.022	.	1.27 (0.93-1.75)	0.136	.
0.78 (0.48-1.25)	0.296	<.001	0.62 (0.42-0.90)	0.012	<.001	0.26 (0.11-0.66)	0.005	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
2.27 (1.80-2.86)	<.001	.	1.53 (1.28-1.83)	<.001	.	3.20 (2.39-4.27)	<.001	.
4.26 (3.39-5.35)	<.001	.	2.42 (2.01-2.91)	<.001	.	8.84 (6.69-11.68)	<.001	.
8.88 (7.01-11.26)	<.001	.	3.87 (3.15-4.74)	<.001	.	24.19 (18.28-32.00)	<.001	.
15.81 (12.10-20.65)	<.001	.	4.36 (3.28-5.79)	<.001	.	45.37 (33.76-60.97)	<.001	.
3.17 (2.05-4.90)	<.001	<.001	6.10 (4.37-8.52)	<.001	<.001	1.47 (0.78-2.78)	0.229	<.001
2.04 (1.61-2.58)	<.001	.	1.74 (1.36-2.23)	<.001	.	1.66 (1.33-2.08)	<.001	.
1.39 (1.17-1.64)	<.001	.	1.12 (0.94-1.35)	0.210	.	1.16 (1.00-1.35)	0.054	.
1.11 (0.96-1.28)	0.171	.	0.99 (0.84-1.15)	0.861	.	1.07 (0.95-1.21)	0.246	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.92 (0.80-1.06)	0.236	.	1.28 (1.12-1.46)	<.001	.	0.96 (0.87-1.07)	0.500	.
0.99 (0.96-1.02)	0.347	.	1.00 (0.97-1.03)	0.931	.	0.99 (0.96-1.02)	0.385	.
1.18 (1.05-1.32)	0.004	.	1.29 (1.15-1.44)	<.001	.	1.14 (1.04-1.25)	0.006	.
1.01 (0.98-1.04)	0.681	.	1.02 (0.99-1.05)	0.256	.	0.98 (0.95-1.01)	0.151	.
1.20 (0.96-1.50)	0.102	0.030	1.38 (1.12-1.70)	0.002	<.001	0.41 (0.29-0.59)	<.001	<.001
1.18 (1.02-1.36)	0.029	.	1.27 (1.09-1.49)	0.003	.	1.19 (1.04-1.36)	0.011	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.00 (0.99-1.01)	0.640	.	1.00 (0.99-1.02)	0.682	.	0.98 (0.97-0.99)	<.001	.
0.57 (0.39-0.83)	0.004	.	0.66 (0.43-0.99)	0.047	.	0.94 (0.76-1.18)	0.603	.

	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	1.49 (1.24-1.80)	<.001	<.001	1.20 (0.85-1.70)	0.297	0.548
18-25	1 (reference)	.	.	1 (reference)	.	.
25-30	1.23 (1.14-1.33)	<.001	.	1.05 (0.92-1.19)	0.457	.
30+	2.03 (1.83-2.24)	<.001	.	1.14 (0.94-1.38)	0.197	.
Hepatitis B virus positive	1.22 (1.09-1.37)	<.001	.	1.02 (0.82-1.27)	0.872	.
Hepatitis C virus positive	1.05 (0.94-1.18)	0.391	.	1.00 (0.81-1.22)	0.962	.
Hypertension	1.13 (1.06-1.21)	<.001	.	1.30 (1.16-1.45)	<.001	.
Smoking status						
Current smoker	1.38 (1.27-1.49)	<.001	<.001	1.75 (1.52-2.00)	<.001	<.001
Never smoker	1 (reference)	.	.	1 (reference)	.	.
Past smoker	1.41 (1.30-1.54)	<.001	.	1.54 (1.34-1.78)	<.001	.
Calendar year period						
2000-2010	1.27 (1.15-1.39)	<.001	<.001	1.40 (1.19-1.65)	<.001	<.001
2011-2015	1.15 (1.06-1.25)	<.001	.	1.22 (1.07-1.39)	0.003	.
2016-2021	1 (reference)	.	.	1 (reference)	.	.
Recent use of ABC ***		.	.	1.58 (1.40-1.79)	<.001	.
Per year longer on LOP/r		.	.	1.01 (0.99-1.02)	0.278	.
Per year longer on IDV		.	.	1.00 (0.99-1.01)	0.919	.
Per year longer on ZDV		.	.		.	.
Per year longer on d4T		.	.		.	.
Per year longer on ddI		.	.		.	.
Per year longer on TAF		.	.		.	.
Per year longer on TDF		.	.		.	.
Prior cardiovascular event		.	.		.	.
Prior diabetes		.	.		.	.
Current use of cobicistat		.	.		.	.
Current use of dolutegravir		.	.		.	.
Current use of rilpivirine		.	.		.	.
Current use of bictegravir		.	.		.	.

**Time-updated.*

***Time-updated and lagged by 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 (1.53-2.51)	<.001	<.001	1.33 (0.91-1.94)	0.139	<.001	1.38 (1.05-1.83)	0.023	0.031
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
0.90 (0.79-1.01)	0.083	.	2.25 (1.97-2.58)	<.001	.	1.14 (1.03-1.25)	0.012	.
0.96 (0.78-1.16)	0.649	.	5.43 (4.67-6.31)	<.001	.	1.13 (0.98-1.30)	0.103	.
1.63 (1.38-1.94)	<.001	.	1.08 (0.88-1.32)	0.475	.	1.44 (1.23-1.69)	<.001	.
1.10 (0.91-1.33)	0.309	.	1.03 (0.84-1.26)	0.793	.	1.32 (1.15-1.53)	<.001	.
0.95 (0.85-1.06)	0.321	.	1.17 (1.05-1.31)	0.004	.	1.10 (1.01-1.20)	0.031	.
1.54 (1.34-1.76)	<.001	<.001	1.02 (0.90-1.17)	0.728	0.002	0.81 (0.73-0.91)	<.001	<.001
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
1.72 (1.50-1.97)	<.001	.	1.24 (1.09-1.42)	0.001	.	1.00 (0.91-1.11)	0.933	.
0.93 (0.80-1.09)	0.386	0.660	1.35 (1.14-1.59)	<.001	<.001	1.34 (1.13-1.58)	<.001	<.001
0.96 (0.84-1.09)	0.501	.	1.28 (1.11-1.47)	<.001	.	1.39 (1.24-1.56)	<.001	.
1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	.	.		.	.		.	.
	.	.		.	.		.	.
	.	.		.	.		.	.
	.	.	1.02 (1.01-1.03)	0.005	.		.	.
	.	.	1.02 (1.00-1.05)	0.108	.		.	.
	.	.	1.06 (1.03-1.08)	<.001	.		.	.
	.	.		.	.	0.99 (0.98-1.01)	0.303	.
	.	.		.	.	1.01 (1.00-1.02)	0.042	.
	.	.		.	.	1.60 (1.39-1.84)	<.001	.
	.	.		.	.	1.33 (1.14-1.54)	<.001	.
	.	.		.	.	1.61 (1.42-1.84)	<.001	.
	.	.		.	.	3.17 (2.85-3.54)	<.001	.
	.	.		.	.	1.34 (1.13-1.59)	<.001	.
	.	.		.	.	2.25 (1.81-2.80)	<.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 2021.*

		All events		0-50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Aspergillosis, invasive pulmonary	9	0.3%	1	0.4%
	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis oropharyngeal	767	26.1%	69	27.9%
	Candidiasis vulvovaginal, frequent/persistent	54	1.8%	1	0.4%
	Cardiomyopathy, HIV-related	5	0.2%	0	0.0%
	Cardiomyopathy, with HIV-related component	17	0.6%	1	0.4%
	Diarrhoea, HIV-related > = 30 days	63	2.1%	1	0.4%
	Fever e.c.i. / HIV-related	6	0.2%	0	0.0%
	HIV-associated nephropathy (HIVAN)	21	0.7%	2	0.8%
	Herpes zoster, multidermatomal	19	0.6%	3	1.2%
	Herpes zoster, recurring / multidermatomal unspecified	211	7.2%	7	2.8%
	Herpes zoster, unidermatomal recurrent	17	0.6%	3	1.2%
	Listeriosis	1	0.0%	0	0.0%
	Myelopathy, HIV-related	10	0.3%	0	0.0%
	Neuropathy, HIV-related	108	3.7%	2	0.8%
	Neuropathy, with HIV-related component	79	2.7%	1	0.4%
	Nocardiosis	2	0.1%	1	0.4%
	Oral Hairy Leucoplakia (OHL)	53	1.8%	2	0.8%
	Pelvic inflammatory disease	9	0.3%	0	0.0%
	Thrombocytopenia, HIV-related	107	3.6%	3	1.2%
	Thrombocytopenia, with HIV-related component	14	0.5%	3	1.2%
	Weight loss >10%, HIV-related / unknown cause	36	1.2%	2	0.8%
Subtotal		**1609**	**54.7%**	**102**	**41.3%**
CDC-C events	AIDS dementia complex - HIV encephalopathy	44	1.5%	5	2.0%
	Bacterial pneumonia, recurring	311	10.6%	11	4.5%
	CMV disease	19	0.6%	4	1.6%
	CMV oesophagitis	1	0.0%	1	0.4%
	CMV retinitis	17	0.6%	4	1.6%
	Candidiasis oesophagitis	237	8.1%	26	10.5%
	Candidiasis lungs/bronchial/trachea	11	0.4%	2	0.8%
	Cervical cancer, invasive	10	0.3%	1	0.4%
	Coccidioidomycosis, extrapulmonary / disseminated	1	0.0%	0	0.0%

CD4 category									
050–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
3	0.5%	0	0.0%	1	0.2%	2	0.3%	2	0.6%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
183	32.2%	159	25.5%	121	21.9%	140	23.2%	95	27.4%
5	0.9%	9	1.4%	18	3.3%	16	2.6%	5	1.4%
1	0.2%	0	0.0%	2	0.4%	1	0.2%	1	0.3%
4	0.7%	2	0.3%	2	0.4%	6	1.0%	2	0.6%
5	0.9%	17	2.7%	10	1.8%	22	3.6%	8	2.3%
1	0.2%	2	0.3%	0	0.0%	1	0.2%	2	0.6%
4	0.7%	3	0.5%	4	0.7%	4	0.7%	4	1.2%
0	0.0%	4	0.6%	2	0.4%	6	1.0%	4	1.2%
25	4.4%	53	8.5%	44	8.0%	51	8.4%	31	8.9%
4	0.7%	0	0.0%	2	0.4%	4	0.7%	4	1.2%
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	0.9%
9	1.6%	17	2.7%	30	5.4%	29	4.8%	21	6.1%
10	1.8%	11	1.8%	18	3.3%	25	4.1%	14	4.0%
0	0.0%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
13	2.3%	11	1.8%	8	1.4%	11	1.8%	8	2.3%
0	0.0%	4	0.6%	0	0.0%	3	0.5%	2	0.6%
20	3.5%	23	3.7%	22	4.0%	27	4.5%	12	3.5%
0	0.0%	5	0.8%	0	0.0%	5	0.8%	1	0.3%
5	0.9%	9	1.4%	6	1.1%	8	1.3%	6	1.7%
297	**52.2%**	**333**	**53.4%**	**290**	**52.4%**	**362**	**59.9%**	**225**	**64.8%**
5	0.9%	8	1.3%	10	1.8%	9	1.5%	7	2.0%
52	9.1%	78	12.5%	80	14.5%	62	10.3%	28	8.1%
2	0.4%	3	0.5%	6	1.1%	1	0.2%	3	0.9%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
5	0.9%	1	0.2%	6	1.1%	1	0.2%	0	0.0%
55	9.7%	56	9.0%	39	7.1%	36	6.0%	25	7.2%
1	0.2%	5	0.8%	1	0.2%	1	0.2%	1	0.3%
2	0.4%	1	0.2%	2	0.4%	4	0.7%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
	Cryptococcosis, extrapulmonary / disseminated	16	0.5%	6	2.4%
	Cryptosporidiosis	11	0.4%	4	1.6%
	Cystoisosporiasis	1	0.0%	0	0.0%
	HIV wasting	17	0.6%	7	2.8%
	HSV chronic ulcer	25	0.8%	1	0.4%
	HSV oesophagitis	1	0.0%	0	0.0%
	HSV pneumonitis	1	0.0%	0	0.0%
	Herpes simplex virus	61	2.1%	7	2.8%
	Histoplasmosis, extrapulmonary / disseminated	4	0.1%	3	1.2%
	Kaposi sarcoma	115	3.9%	7	2.8%
	Leishmaniasis visceral	5	0.2%	1	0.4%
	Microsporidiosis	5	0.2%	2	0.8%
	Mycobacterium avium/kansasii, extrapulmonary / disseminated	22	0.7%	4	1.6%
	Mycobacterium avium/kansasii, pulmonary	3	0.1%	0	0.0%
	Mycobacterium other / unspecified, extrapulmonary / disseminated	9	0.3%	3	1.2%
	Mycobacterium other / unspecified, pulmonary	5	0.2%	0	0.0%
	Non-Hodgkin's lymphoma (NHL)	153	5.2%	6	2.4%
	Pneumocystis jirovecii extrapulmonary	1	0.0%	0	0.0%
	Pneumocystis jirovecii pneumonia	69	2.3%	19	7.7%
	Primary CNS lymphoma	6	0.2%	1	0.4%
	Progressive multifocal leukoencephalopathy	18	0.6%	5	2.0%
	Toxoplasmosis of the brain	20	0.7%	8	3.2%
	Tuberculosis, extrapulmonary / disseminated	46	1.6%	3	1.2%
	Tuberculosis, pulmonary	70	2.4%	4	1.6%
Subtotal		**1335**	**45.3%**	**145**	**58.7%**
Total		**2944**	**100.0%**	**247**	**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	%
	7	1.2%	2	0.3%	0	0.0%	1	0.2%	0	0.0%
	0	0.0%	1	0.2%	3	0.5%	2	0.3%	1	0.3%
	0	0.0%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	6	1.1%	1	0.2%	2	0.4%	1	0.2%	0	0.0%
	4	0.7%	1	0.2%	2	0.4%	12	2.0%	5	1.4%
	0	0.0%	0	0.0%	1	0.2%	0	0.0%	0	0.0%
	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
	6	1.1%	13	2.1%	16	2.9%	15	2.5%	4	1.2%
	0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
	11	1.9%	24	3.8%	28	5.1%	32	5.3%	13	3.7%
	3	0.5%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
	2	0.4%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
	9	1.6%	5	0.8%	2	0.4%	1	0.2%	1	0.3%
	0	0.0%	1	0.2%	0	0.0%	1	0.2%	1	0.3%
	2	0.4%	3	0.5%	0	0.0%	1	0.2%	0	0.0%
	2	0.4%	0	0.0%	2	0.4%	1	0.2%	0	0.0%
	40	7.0%	36	5.8%	32	5.8%	27	4.5%	12	3.5%
	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
	24	4.2%	11	1.8%	7	1.3%	7	1.2%	1	0.3%
	2	0.4%	2	0.3%	1	0.2%	0	0.0%	0	0.0%
	6	1.1%	4	0.6%	2	0.4%	1	0.2%	0	0.0%
	6	1.1%	4	0.6%	1	0.2%	1	0.2%	0	0.0%
	9	1.6%	7	1.1%	5	0.9%	12	2.0%	10	2.9%
	11	1.9%	22	3.5%	15	2.7%	11	1.8%	7	2.0%
	272	**47.8%**	**291**	**46.6%**	**263**	**47.6%**	**242**	**40.1%**	**122**	**35.2%**
	569	**100.0%**	**624**	**100.0%**	**553**	**100.0%**	**604**	**100.0%**	**347**	**100.0%**