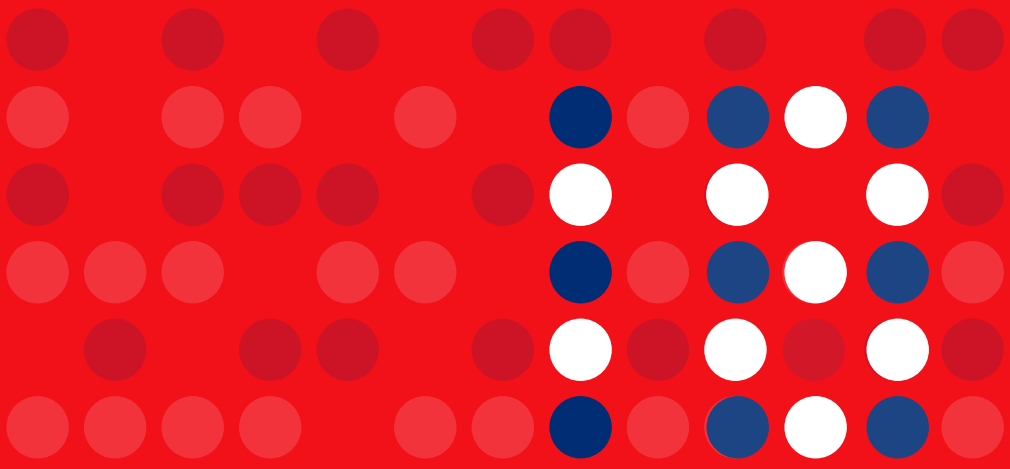
Human Immunodeficiency Virus (HIV)
infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2018

Chapter 3: Morbidity and mortality



About Stichting HIV Monitoring

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

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

In addition to national reports, healthcare professionals are provided with treatment centre-specific reports to enable them to monitor and optimise care provided in their centres. Moreover, upon request, SHM data are also made available for use in HIV-related research, both in the Netherlands and internationally. The outcome of SHM's research and international collaborations provides tangible input into policy guidelines and further improves HIV care in the Netherlands.

Our mission

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

HIV Monitoring

Monitoring Report 2018

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

Interactive PDF user guide

This PDF allows you to find information and navigate around this document more easily.

Links in this PDF

Words and numbers that are underlined are links — clicking on them will take you to further information within the document or to a web page (which opens in a new window) if they are a url (e.g http://www.cdc.gov/hiv/guidelines/).

Reference numbers

Click on the reference numbers in the text to see the reference details on a web page (which opens in a new window).

Guide to buttons

Content page

Next chapter

Preceding chapter

You can also navigate using the bookmarks.

Acknowledgements

Authors: Ard van Sighem, Sonia Boender, Ferdinand Wit, Colette Smit, Amy Matser, Peter Reiss

Co-authors: Joop Arends, Ward van Bilsen, Kees Brinkman, Ashley Duits, Suzanne Geerlings, Gonneke Hermanides, Frank Kroon, Kees van Nieuwkoop, Eline Op de Coul, Jan Prins, Maria Prins, Clemens Richter, Annemarie van Rossum, Marc van der Valk, Anne Wensing, Diederik van de Wetering, Tom Wolfs

Production and support: Catriona Ester, Mireille Koenen, Yunka de Waart

Requests for digital copies: Stichting HIV Monitoring, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands
T +31 20 5664172
E: hiv.monitoring@amc.uva.nl, www.hiv-monitoring.nl

Visiting address: Stichting HIV Monitoring, Nicolaes Tulphuis, Tafelbergweg 51, 1105 BD Amsterdam, the Netherlands

KvK#: 34160453
Correspondence to: Peter Reiss, hiv.monitoring@amc.uva.nl

To cite this report, please use: van Sighem A.I., Boender T.S., Wit F.W.N.M., Smit C., Matser A., Reiss P. Monitoring Report 2018. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring, 2018. Available online at www.hiv-monitoring.nl

ISBN/EAN: 978-94-90540-09-8
First edition: November 2018
Editing: Sally H. Ebeling, Boston, MA, USA

Art Direction & DTP: Studio Zest, Wormer, the Netherlands

3. Morbidity and mortality

Ferdinand Wit, Marc van der Valk and Peter Reiss

Introduction

Of the 25,761 HIV-1-positive adults and children ever registered in the Dutch national HIV registration and monitoring database up to 31 December 2017, 95.0% are currently on combination antiretroviral therapy (cART). Since the introduction of cART, the life expectancy of HIV-1-positive individuals has markedly improved; in a subgroup of recently-diagnosed, effectively-treated individuals, it has been shown to be similar to that of the general population in the Netherlands[1].

Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased[2], morbidity and/or mortality associated with non-AIDS-related diseases such as renal and liver disease, diabetes mellitus, myocardial infarction, stroke, osteoporosis, and non-AIDS-defining malignancies has increased among HIV-1 positive individuals during the cART era[3,4,5,6,7,8].

Various reports suggest that the risk of non-AIDS morbidity may be higher in HIV-positive individuals treated with antiretroviral therapy (ART) than in HIV-negative individuals of comparable age[9,10,11]. For example, pulmonary hypertension[12], bone disease, and non-traumatic bone fractures[13,14,15] have been reported to be more common in HIV-1-positive individuals. There is also a concern that HIV-related neurocognitive impairment may persist or even progress, despite otherwise effective long-term cART[16,17,18]. Furthermore, as in HIV-negative individuals, traditional risk factors (e.g., tobacco use[19], alcohol abuse, and viral hepatitis co-infection[20]) are likely to also importantly contribute to the increased risk of certain non-AIDS comorbidities in people living with HIV.

Importantly, one of the most prevalent comorbidities is cardiovascular disease (CVD). In addition to traditional risk factors such as smoking, probable additional risk factors with high prevalence among HIV-1-positive individuals include metabolic abnormalities, such as dyslipidaemia, insulin resistance, hypertension, diabetes, and changes in body fat distribution (lipodystrophy), which may be driven partly by the use of cART, as well as by sustained residual HIV-associated immune activation and inflammation, despite effective cART[21,22].

In this chapter, we report on mortality and causes of death for adult (18 years and older) HIV-1-positive individuals using updated Stichting HIV Monitoring (SHM) data: 25,065 adults and an additional 459 individuals who entered care as children

and have since become adults, now totalling 25,524 adult individuals. In addition, we report on the incidence of AIDS and non-AIDS comorbidities, particularly diabetes mellitus, cardiovascular disease, chronic kidney disease (CKD), and non-AIDS malignancies in HIV-1-positive individuals.

Definitions

AIDS is defined as the presence of any Centers for Disease Control (CDC) category C condition[23]). A CD4 count below 200 cells/mm^3 in the absence of an AIDS-defining condition, in contrast to what is usual in the United States, does not qualify as AIDS in these analyses.

Diabetes mellitus is defined according to criteria established by the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study.

Cardiovascular disease, including myocardial infarction, stroke, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy, is also defined according to criteria established by the D:A:D study.

Non-AIDS-defining malignancies, excluding precancerous stages of anal and cervical cancer, basal cell carcinoma, and squamous cell carcinoma of the skin, are defined according to criteria established by the D:A:D study, except that Castleman's disease is also defined as a non-AIDS-defining malignancy. Histological confirmation of malignancies is part of standard clinical practice in the Netherlands, and therefore, pathology reports have been used wherever possible to establish the presence of any malignancy.

Chronic kidney disease (CKD) is defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min (estimated with the Cockcroft-Gault equation), confirmed after 6 months or longer. In previous Monitoring Reports we used a period of 3 months, but in the present Monitoring Report, we have extended the period to 6 months because of the large number of CKD episodes that revert shortly after 3 months.

Methods

For the analyses of incidence per calendar year and period, we consider all events after an individual entered care following HIV-1 diagnosis or after the start of routine collection of data on the condition of interest, whichever occurred more recently. For instance, data on CKD were analysed from April 2007 onwards, because that was when routinely-collected renal laboratory data became available for analysis. As the average age of the Dutch HIV population has increased over

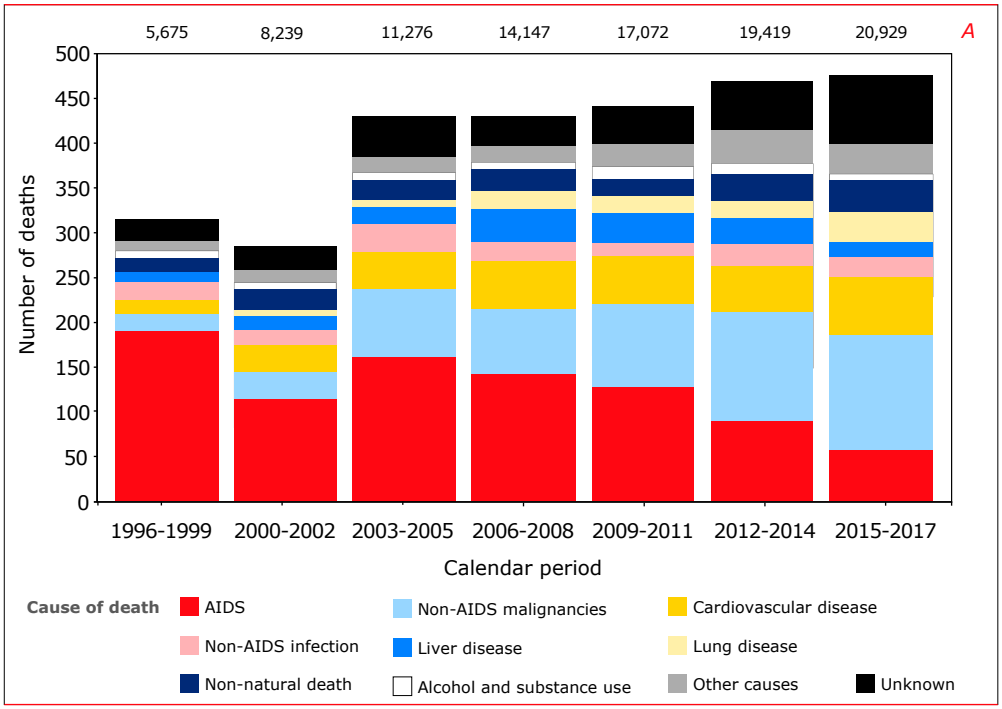
time, we also estimated the incidence rates for the periods 2000-2005, 2006-2010, and 2011-2017, and standardised these according to the age distribution of the population during the period 2011-2017 (divided into age classes 18-29, 30-39, 40-49, 50-59, 60-69, and ≥70 years) using the indirect method[24]. Indirect standardisation compares the incidence rates in the study and reference (period: 2011-2017) populations by applying the stratum-specific rates in the reference population to the study population. We investigated risk factors for AIDS, death, and each of the non-AIDS events, as well as a combined non-AIDS endpoint (defined as first occurrence of cardiovascular disease, diabetes mellitus, or non-AIDS-defining malignancy). CKD was not included in this combined endpoint as serum creatinine was not part of routine data collection before 2007. The baseline for treated and untreated HIV-1-positive individuals was defined as the date of HIV-1 diagnosis or January 2000, whichever occurred more recently. Subsequent follow-up time was divided into periods of 3 months. Poisson regression models were used to estimate the independent association between risk factors and each endpoint. Models were adjusted for most recent CD4 cell count (lagged by 3 months), body mass index, gender, region of birth, most likely mode of HIV-1 transmission, current age, known time with CD4 count <200 cells/mm^3, known time with plasma HIV RNA >1000 copies/ml while on cART, time on cART, specific antiretroviral drugs used, prior diagnosis of AIDS, presence of chronic active hepatitis B and/or C virus infection, hypertension, smoking, and calendar period.

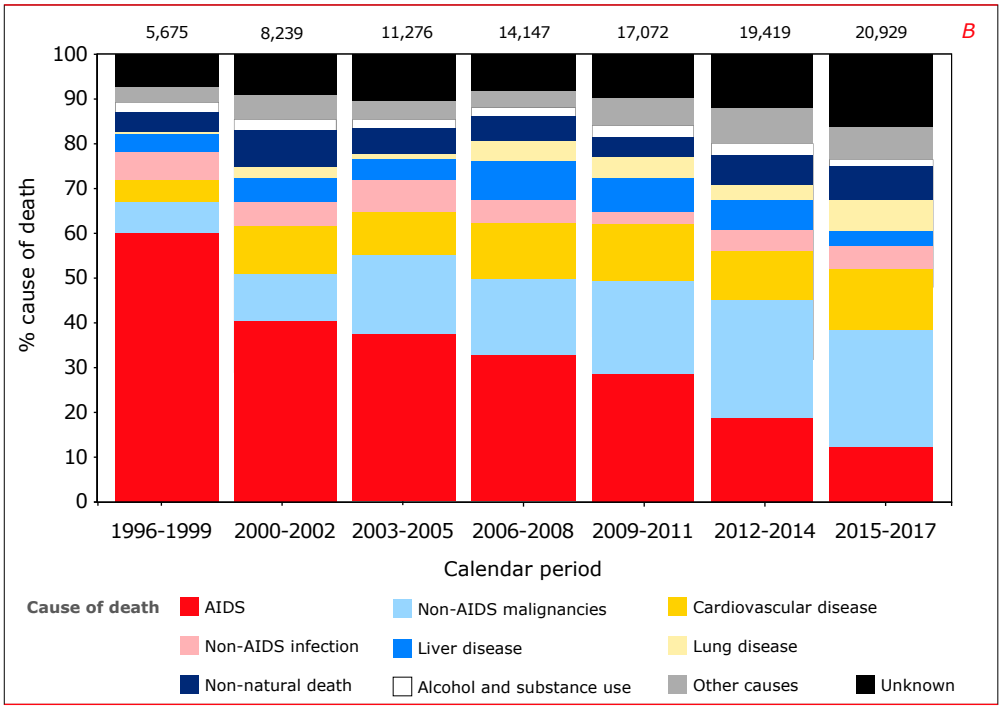
Mortality and AIDS

From 1996 onwards, the overall mortality rate in all 25,761 HIV-1-positive adults ever registered in the SHM was 17.7 (95% confidence interval [CI] 13.1-23.2) per 1,000 person years of follow up (PYFU) in 1996 and declined over time to 7.5 (95% CI 6.3-8.9) per 1,000 PYFU in 2017 (*Appendix Figure 3.1A*; *Appendix Table 3.1*). Despite this improvement over time, the mortality rate in HIV-1-positive adults remains well above that expected for the general population in the Netherlands, which was 4.1 per 1,000 PYFU in 2017, when matched in terms of age and gender of the HIV-positive population. The excess mortality rate can be partly ascribed to individuals who already had AIDS at the time of their HIV diagnosis. When these individuals were excluded, the mortality rate was 11.8 (95% CI 11.3-12.2) per 1,000 PYFU overall (period, 1996-2017) and 6.8 (95% CI 5.5-8.3) per 1,000 PYFU in 2017. In the same group of 25,761 individuals, the incidence of AIDS decreased sharply from 118.0 (95% CI 105.8-131.2) in 1996 to 6.7 (95% CI 5.5-8.0) cases per 1,000 PYFU in 2017 (*Appendix Figure 3.1B*).

Observed underlying causes of death are presented in *Appendix Table 3.2*. Although the AIDS-related death rate has decreased significantly since the advent of cART, it still remains substantial and is probably driven largely by the high number of individuals still presenting late for care with already advanced immune deficiency. Thirty-five per cent of all individuals who died of AIDS between 2011 and 2017 had a CD4 cell count <50 cells/mm^3 when entering care. Individuals who died of AIDS had lower CD4 counts (median 94 cell/mm^3 [interquartile range, IQR, 22-306]) when entering care compared to individuals who died of another cause (median 260 cells/mm^3 [IQR 92-474]). Among individuals who entered care with more than 300 CD4 cells/mm^3 and died of AIDS, the cause of death was relatively more likely to be an AIDS-related malignancy (27.7%) than among individuals who entered care with less than 50 CD4 cells/mm^3 (18.8%). The time between entry into care and death was significantly shorter in individuals who died of AIDS (median 3.4 years [IQR 0.6-8.9]) than in individuals who died of a non-AIDS cause (median 8.7 years [IQR 4.3-14.7], p<0.001). Conversely, the proportion and absolute number of deaths due to non-AIDS-defining conditions have significantly increased over time (*Figure 3.1A* and *B*), partly as a consequence of the increasing size and average age of the Dutch HIV-positive population.

Figure 3.1A and B: (A) Absolute and (B) relative changes in causes of death in different calendar periods since the introduction of combination antiretroviral therapy (cART) in the Netherlands. The numbers at the top of each bar represent the number of individuals that were at risk during that calendar period. Mortality attributed to 'alcohol use' consisted of deaths due to complications of alcohol-related liver cirrhosis.





We used Poisson regression analysis to examine factors associated with death in individuals from the moment of starting cART. After correction for all variables listed in *Appendix Table 3.3*, including time-updated age and time-updated lagged CD4-cell counts, the risk ratios for a number of possible risk factors are presented in *Appendix Table 3.3*. In general, men were more likely to die than women, and an individual's risk of death increased if they were older, belonged to the HIV transmission risk group of people who use/used injecting drugs (PWUID), had been pre-treated with nucleoside-analogue reverse transcriptase inhibitors (NRTIs) at the start of cART, had a prior AIDS diagnosis, were co-infected with HBV or HCV, were underweight, were current or past smokers, had spent more time with an HIV RNA level above 1,000 copies/ml while on cART, or had a current CD4 cell count less than 500 cells/mm^3 (although the risk of death was even higher when their CD4 cell count was less than 200 cells/mm^3). Of note, people with a CD4 cell count above 750 cells/mm^3 had a significantly lower mortality risk than those with a CD4 cell count between 500 and 750 cells/mm^3. People who had initiated cART early, i.e. within 12 months of their last negative HIV test or within 12 months after documented acute

HIV infection, had a borderline lower risk of death compared with those who initiated cART at a later time point or who had an unknown duration of HIV infection prior to initiation of cART. Note that this beneficial effect of early cART was independent of the CD4 cell count.

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

The incidence of the first occurrence of any AIDS-defining event after entering care was 23.7 events per 1,000 PYFU of follow up. *Appendix Table 3.5* gives an overview of the AIDS events occurring between 1996 and 2017. The most common AIDS events between 2011 and 2017 were *Pneumocystis jirovecii* pneumonia (21% of all events), oesophageal candidiasis (17%), Kaposi's sarcoma (11%), tuberculosis (pulmonary 8%, extrapulmonary 5%), lymphoma (6%), toxoplasmosis of the brain (5%), AIDS-related wasting (5%), recurrent bacterial pneumonia (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 3.3*. In the present analyses, we concentrate on the first occurrence of any AIDS-defining event after the start of cART. The results of these analyses show that individuals were more likely to experience their first AIDS-defining event if they were older, had a current CD4 cell count below 500 cells/mm^3 (but the likelihood was even higher when their CD4 cell count was below 200 or 50 cells/mm^3), had more than 1,000 HIV RNA copies/ml for a longer period of time while on cART, or were co-infected with the hepatitis C virus.

Because the main findings of the analysis of AIDS events after start of cART were heavily influenced by events occurring shortly after the start of cART and/or while HIV-1 viraemia was detectable, we also analysed the incidence of CDC-B and AIDS-defining events in the period between 2000 and 2017 in individuals who had started cART at least 1 year before and had undetectable viraemia (or transient low

level viraemia, i.e. 'blips' below 200 copies/ml) at the moment the HIV-related event was diagnosed. Therefore, this analysis focuses on those individuals with an optimal response to cART. Events were classified into CD4 strata based on the current CD4 and previously measured CD4 count, whichever was the lowest. Use of prophylaxis was not accounted for in this analysis. Only 'definitive' or 'probable' diagnoses were considered; 'possible' events or events with incomplete ascertainment data were excluded from the analysis. Between 1 January 2000 and 31 December 2017, 21,984 individuals contributed a total of 151.4 thousand PYFU, during which 2,875 HIV-related events were diagnosed, resulting in an incidence rate of 19.0 events per 1,000 PYFU (1,787 CDC-B events, 11.8 events/1,000 PYFU; 1,088 CDC-C/AIDS events, 7.2 events/1,000 PYFU) (*Table 3.1*). As expected, the incidence rates were highest in the CD4 strata below 200 cells/mm^3. Although the incidence rates declined sharply in the higher CD4 strata, the incidence rates in the 200-349 and 350-499 cells/mm^3 strata remained substantial, with 11.9 and 6.2 AIDS-defining illnesses/1000 PYFU, respectively. The incidence rates of AIDS-defining illnesses in the CD4 strata of 500-749 and over 750 cells/mm^3 were 3.4 (3.0-4.0) and 2.3 (1.8-2.9)/1,000 PYFU, respectively. Note that the incidence in the 750+ stratum is statistically significantly lower than in the 500-749 cells/mm^3 stratum. In these highest CD4 strata the main AIDS-defining events that still occurred were recurrent bacterial pneumonia, Kaposi's sarcoma, oesophageal candidiasis, non-Hodgkin's lymphoma, tuberculosis (pulmonary and extrapulmonary), chronic genital HSV ulcers, and AIDS dementia complex (*Appendix Table 3.8* shows the type and number of HIV-related diagnoses by CD4 strata).

Table 3.1: *CDC-B and CDC-C/AIDS events occurring in individuals on cART while having an undetectable viral load between 2000 and 2016.*

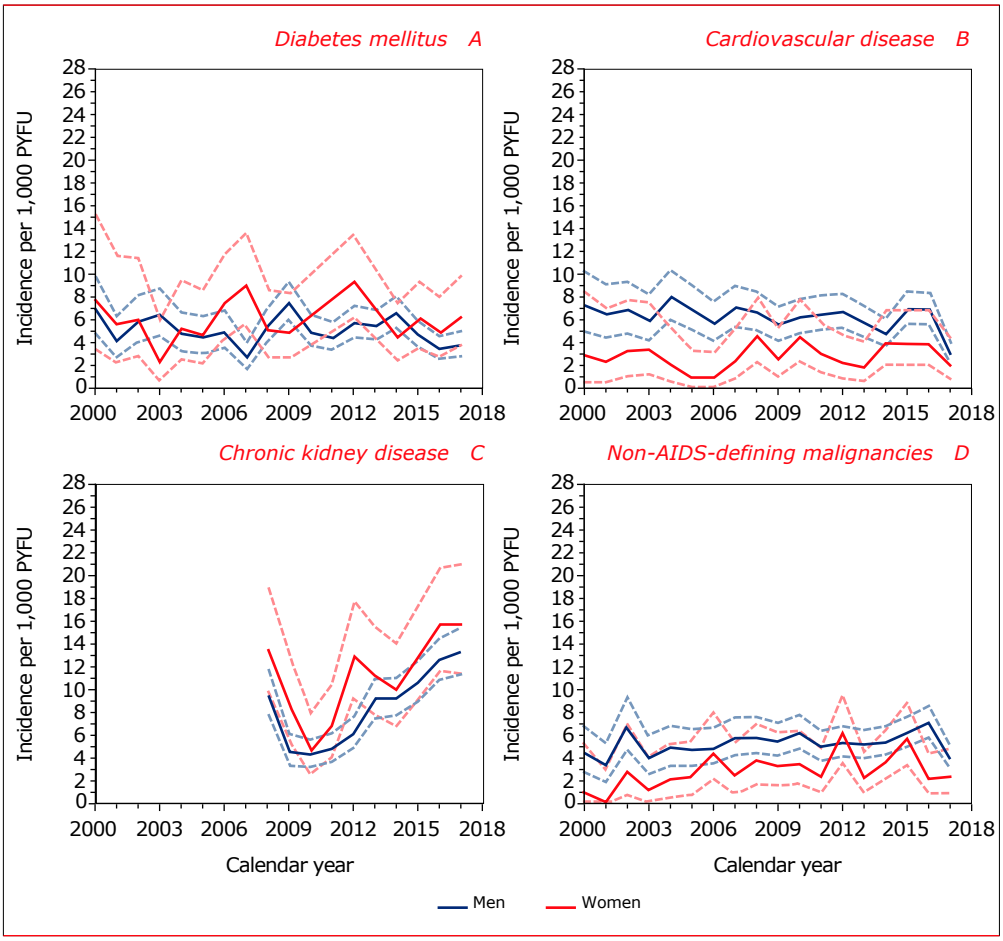
CD4 category (cells/mm^3)	CDC events (n)	CDC-B events (n)	CDC-C events (n)	PYFU (x 1,000)	Incidence rate CDC events (per 1,000 PYFU) (95% CI)	Incidence rate CDC-B events (per 1000 PYFU) (95% CI)	Incidence rate CDC-C events (per 1,000 PYFU) (95% CI)
0-49	212	88	124	0.4	506 (440-579)	210 (168-259)	296 (246-353)
50-199	556	312	244	7.3	76.5 (70.3-83.2)	43.0 (38.3-48.0)	33.6 (29.5-38.1)
200-349	657	400	257	22.2	29.6 (27.4-32.0)	18.0 (16.3-19.9)	11.6 (10.2-13.1)
350-499	580	363	217	36.9	15.7 (14.5-17.0)	9.83 (8.85-10.9)	5.88 (5.12-6.71)
500-749	604	417	187	58.3	10.4 (9.55-11.2)	7.15 (6.48-7.87)	3.21 (2.76-3.70)
750+	338	250	88	41.6	8.13 (7.29-9.05)	6.01 (5.29-6.81)	2.12 (1.70-2.61)
Total	**2,947**	**1,830**	**1,117**	**166.7**	**17.7 (17.0-18.3)**	**11.0 (10.5-11.5)**	**6.70 (6.31-7.11)**

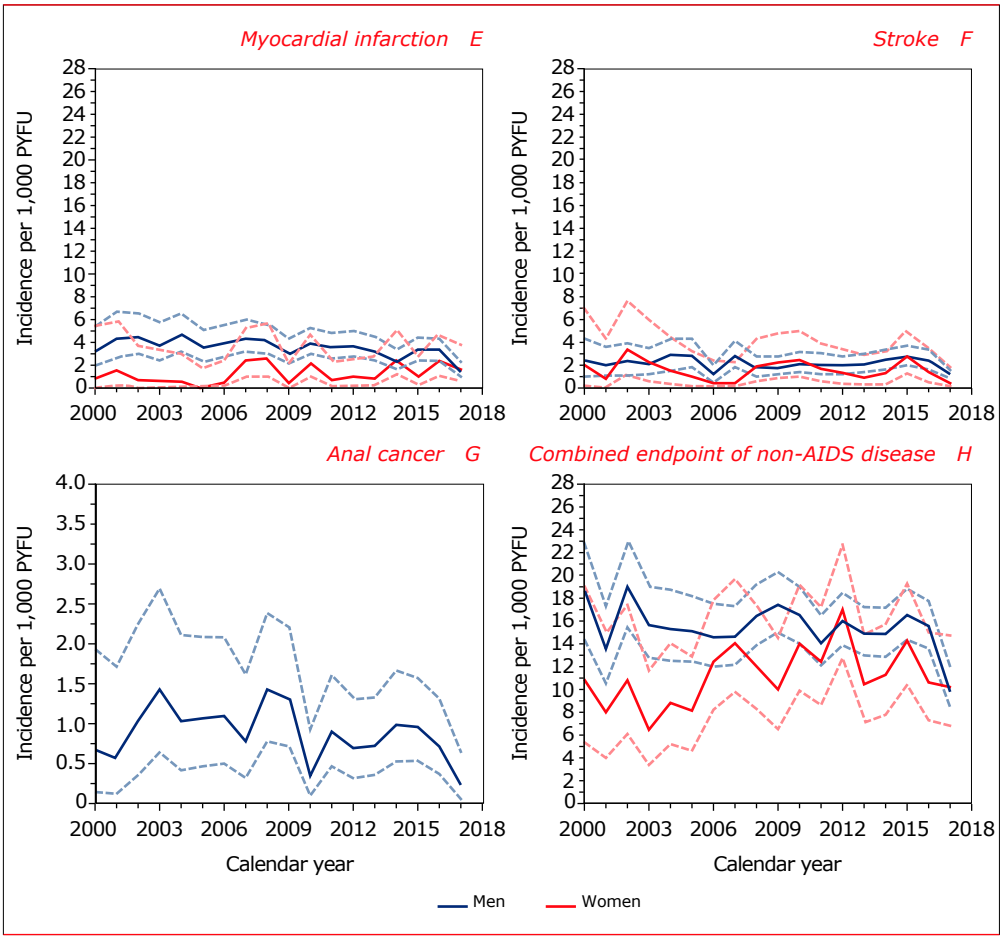
Legend: *CDC=Centers for Disease Control and Prevention Classification System for HIV Infection; CDC-B=moderately symptomatic HIV disease; CDC-C=AIDS-defining events; cART=combination antiretroviral therapy; PYFU=person years of follow up.*

Non-AIDS-defining events

Of the 25,761 HIV-1-positive adults ever registered with the Dutch national HIV registration and monitoring database, 25,178 were aged 18 years or older while in follow up in or after January 2000. For these treated and untreated adults, we report incidence figures and risk factors for diabetes mellitus, a composite cardiovascular disease endpoint (with separate reports for myocardial infarction and stroke), non-AIDS-defining malignancies (with a separate report for anal cancer), and CKD. We also present the incidence of the first occurrence of diabetes mellitus, cardiovascular disease, or non-AIDS-defining malignancies as a combined non-AIDS disease endpoint (*Figure 3.2*; *Appendix Table 3.6A-H*).

Figure 3.2: *Crude incidence rates per 1,000 person years of follow up (solid lines) and 95% confidence intervals (dotted lines) of (A) diabetes mellitus, (B) cardiovascular disease, (C) chronic kidney disease, (D) non-AIDS-defining malignancies, (E) myocardial infarction, (F) stroke, (G) anal cancer, and (H) combined endpoint of non-AIDS disease (diabetes mellitus, cardiovascular disease, and non-AIDS-defining malignancies), by gender, with the exception of anal cancer, which is presented for males only.*





Legend: *PYFU=person years of follow up.*

Diabetes mellitus

Of the 25,178 individuals aged 18 years or older and in follow up in or after January 2000, a total of 1,178 (906 men and 272 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.2A*) and, in 2017, was 3.8 (95% CI 2.8-5.0) per 1,000 PYFU of follow up in men and 6.2 (95% CI 3.7-9.9) per 1,000 PYFU in women. In both men and women, the incidence increased with older age (*Appendix Table 3.6A*). In men, the age-standardised incidence ratio declined over time and was significantly lower in 2011-2017 than in 2000-2005 and 2006-2010. In women, the age standardised incidence in 2000-2005 and 2006-2010 was not significantly different from that in 2011-2017 (*Table 3.2*).

Demographic and clinical factors independently associated with increased risk of new-onset diabetes mellitus were male gender, non-Dutch origin (in particular people born in sub-Saharan Africa, South Asia, and the Caribbean), older age, having acquired HIV heterosexually or through injecting drug use, having a BMI greater than 25 kg/m^2 or below 18 kg/m^2, having hypertension, having a latest CD4 cell count below 200 cells/mm^3, being pre-treated with NRTIs at the start of cART, and a prior AIDS diagnosis (*Appendix Table 3.7*). Moreover, the risk of new-onset diabetes in the periods 2000-2005 and 2006-2010 was significantly higher than in the period 2011-2017. Finally, a longer time on zidovudine was also significantly associated with an increased risk.

Table 3.2: *Crude incidence of diabetes mellitus per 1,000 person years of follow up during 2000–2005, 2006–2010 and 2011–2017 and age-standardised incidence ratio (indirect method) with 95% confidence intervals.*

Calendar year	Men		Women	
	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)
2000–2005	5.4 (4.7–6.2)	1.42 (1.22–1.63)	5.0 (3.7–6.6)	0.81 (0.58–1.04)
2006–2010	5.2 (4.6–5.9)	1.22 (1.07–1.37)	6.5 (5.2–8.0)	1.03 (0.81–1.25)
2011–2017	4.9 (4.4–5.3)	1 (reference)	6.6 (5.5–7.7)	1 (reference)

**Standardised according to the observed age distribution between 2011–2017.*

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

Cardiovascular disease

From January 2000 onwards, 1,226 individuals (1,092 men and 134 women) had a fatal or non-fatal cardiovascular event (644 had myocardial infarction, 437 stroke, 85 coronary artery bypass graft, 415 coronary angioplasty or stenting, and 10 carotid endarterectomy). The crude incidence over time remained stable and was lower in women than in men (*Figure 3.2B*). The incidence in both men and women increased with older age (*Appendix Table 3.6B*). The standardised incidence ratio in men declined over time, whereas in women the standardised incidence in 2000-2005 and 2006-2010 was not significantly different from that in 2011-2017 (*Table 3.3*).

In the analysis of risk factors, those associated with cardiovascular disease were male gender, Dutch origin, older age, acquiring HIV through MSM contacts or through injecting drug use, a latest CD4 cell count <350 cells/mm^3, having a prior AIDS diagnosis, being pre-treated with NRTIs at the start of cART, use of abacavir (either currently or in the last 6 months), current and past smoking, and presence of hypertension. Cardiovascular risk was also higher during 2000-2005 and 2006-2010 than during 2011-2017, independent of other variables included in the analysis (*Appendix Table 3.7*). The strong positive association between use of abacavir and CVD was independent of renal function. When eGFR estimated using the Cockcroft-Gault method (available from 2007 onwards) was included into the model, the abacavir effect was only slightly attenuated from an incidence risk ratio (IRR) of 1.54 to one of 1.44, p<0.001. Having an eGFR below 90 ml/min was independently associated with a higher risk for CVD; at 60-90 ml/min, the IRR was 1.28 (95% CI 1.09-1.52), p=0.003; at 30-60 ml/min the IRR was 1.80 (1.35-2.32), p<0.001; at 15-30 ml/min, the IRR was 5.19 (3.06-8.78) p<0.001; and at 0-15 ml/min the IRR was 4.37 (2.04-8.78), p<0.001.

From January 2000 onwards, 149 men and 11 women experienced a fatal or non-fatal secondary cardiovascular event (103 had myocardial infarction, 63 had stroke). The crude incidence per 1,000 PYFU over the whole period between 2000 and 2016 in men and women with a prior cardiovascular event was 27.8 (95% CI 23.5-32.6) and 15.6 (95% CI 7.8-27.9), respectively. The crude rate and age-standardised incidence ratio (SIR; indirect method) of secondary myocardial infarction and stroke per 1,000 PYFU did not change significantly during 2000-2005 (crude rate: 36.8 events per 1,000 PYFU; SIR: 1.58 95% CI 1.05-2.10) and 2006-2010 (crude rate: 27.9 events per 1,000 PYFU; SIR: 1.19, 95% CI 0.83-1.56) compared to the reference period 2011-2017 (crude rate: 22.9 events per 1,000 PYFU).

Table 3.3: Crude incidence of cardiovascular disease per 1,000 person years of follow up between 2000-2005, 2006-2010, and 2011-2017 and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Men		Women	
	Incidence/1000 PYFU (95%CI)	Standardised incidence ratio* (95% CI)	Incidence/1000 PYFU (95%CI)	Standardised incidence ratio* (95% CI)
2000-2005	6.9 (6.1-7.9)	1.77 (1.55-1.99)	2.4 (1.5-3.6)	1.15 (0.68-1.61)
2006-2010	6.2 (5.5-7.0)	1.32 (1.17-1.47)	3.2 (2.3-4.3)	1.30 (0.91-1.70)
2011-2017	5.8 (5.3-6.3)	1 (reference)	3.1 (2.4-3.9)	1 (reference)

**Standardised according to the observed age distribution between 2011-2017.*

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

Trends in cardiovascular risk factors

The percentage of men with a cholesterol level of 6.2 mmol/l or higher has decreased over time from 26% of those with an available cholesterol measurement in 2000 (regardless of whether statins were used) to 11% in 2017 (*Figure 3.3*). In women, this figure decreased from 19% in 2000 to a minimum of 12% in 2007 and has since increased somewhat to 15% in 2017.

Figure 3.3: Distribution of cholesterol levels (mmol/l) at the end of each calendar year in (A) men and (B) women as a percentage of the total number of men and the total number of women, respectively, with an available cholesterol measurement. 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.

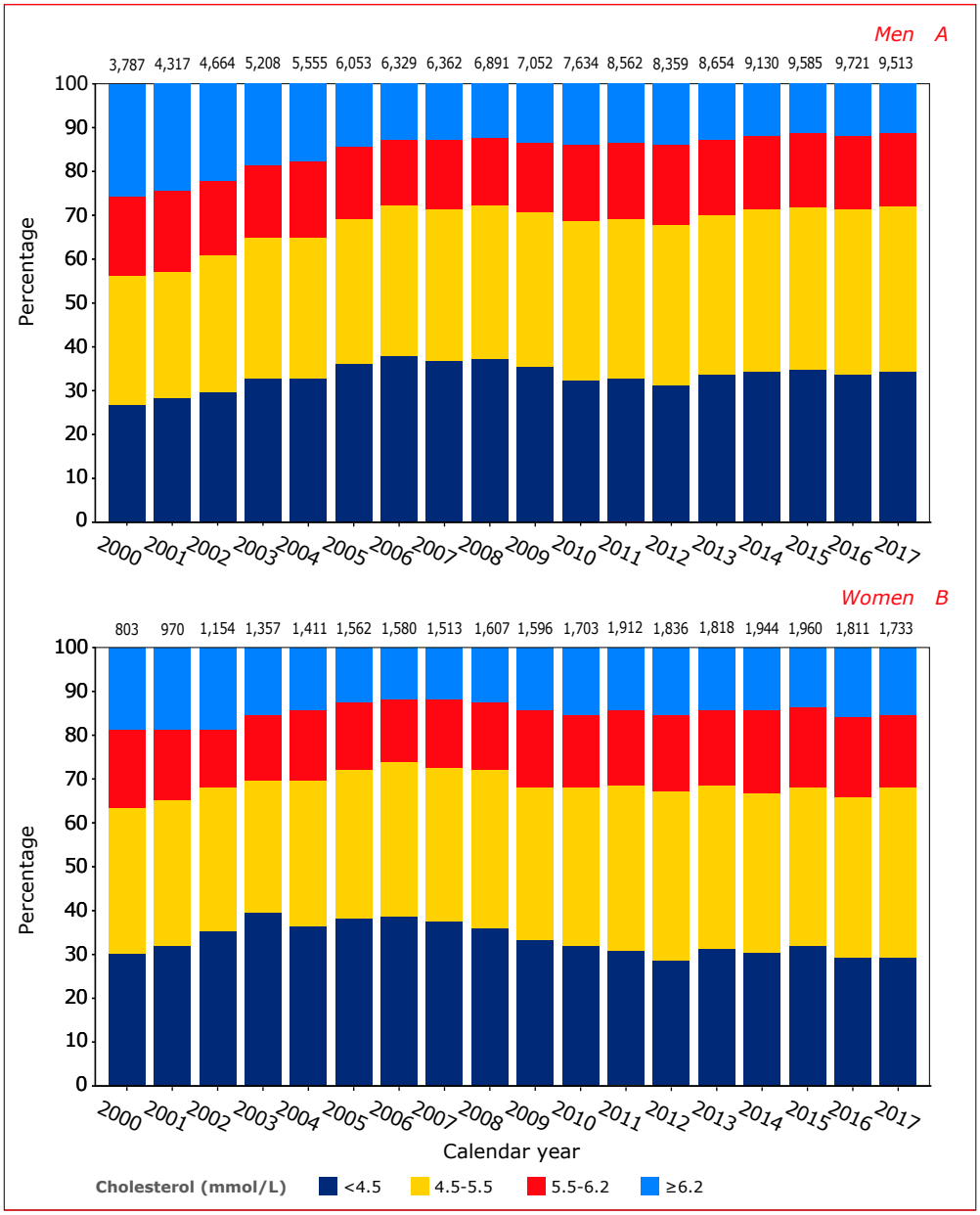
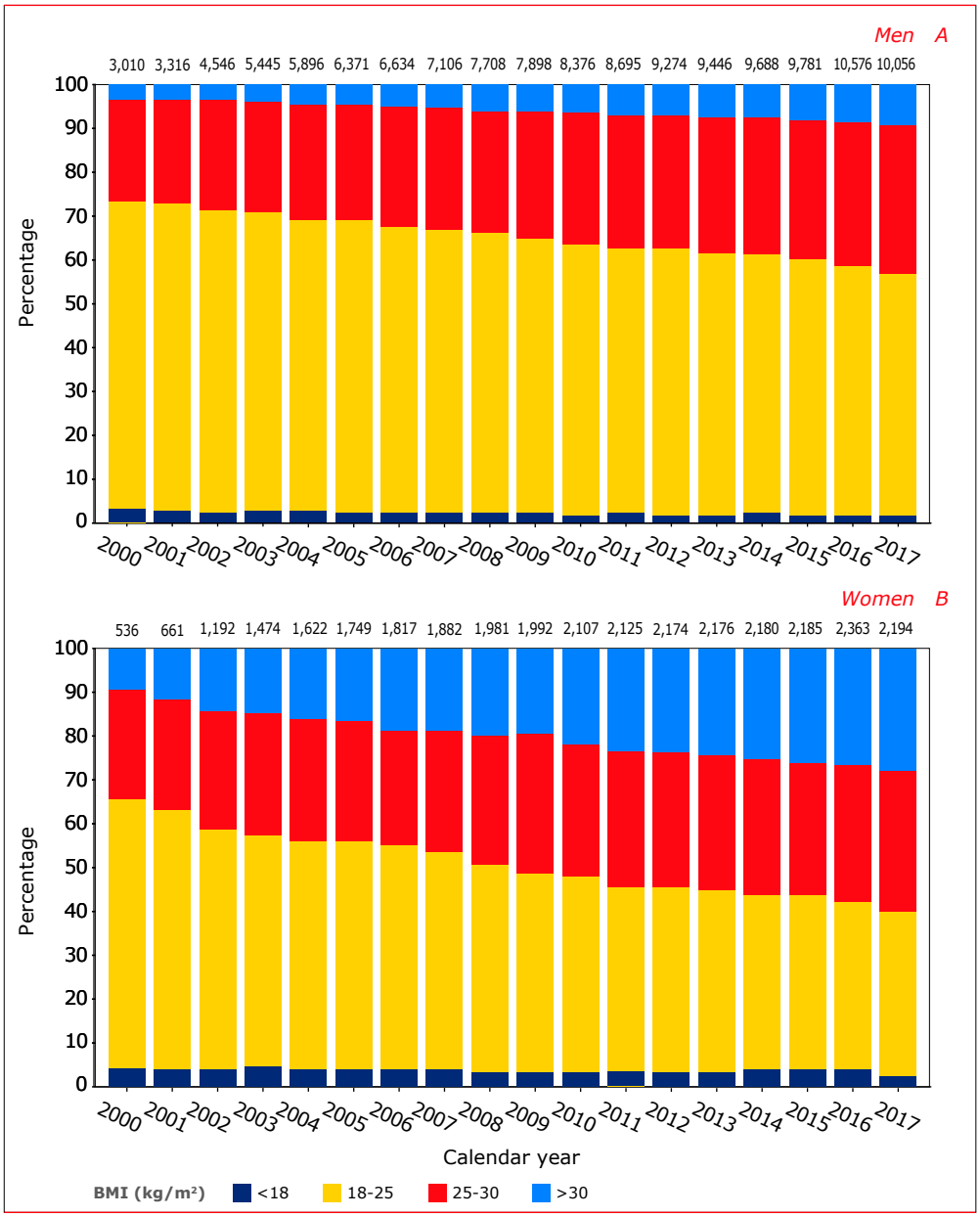


Figure 3.4 shows that the distribution of body mass index (BMI) of both men and women in the HIV-1-positive population has increased over time. In 2017, the percentage of overweight (25-30 kg/m^2) and obese (≥30 kg/m^2) men with an available BMI measurement was 34% and 9%, respectively. In women, these percentages were 31% and 29%, respectively. Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the HIV-positive population. This analysis revealed that the increase in BMI over time was at least partially driven by changes over time in population demographic characteristics (age, region of origin, transmission risk group) and time since first start of cART, and that this effect was more marked in men than in women.

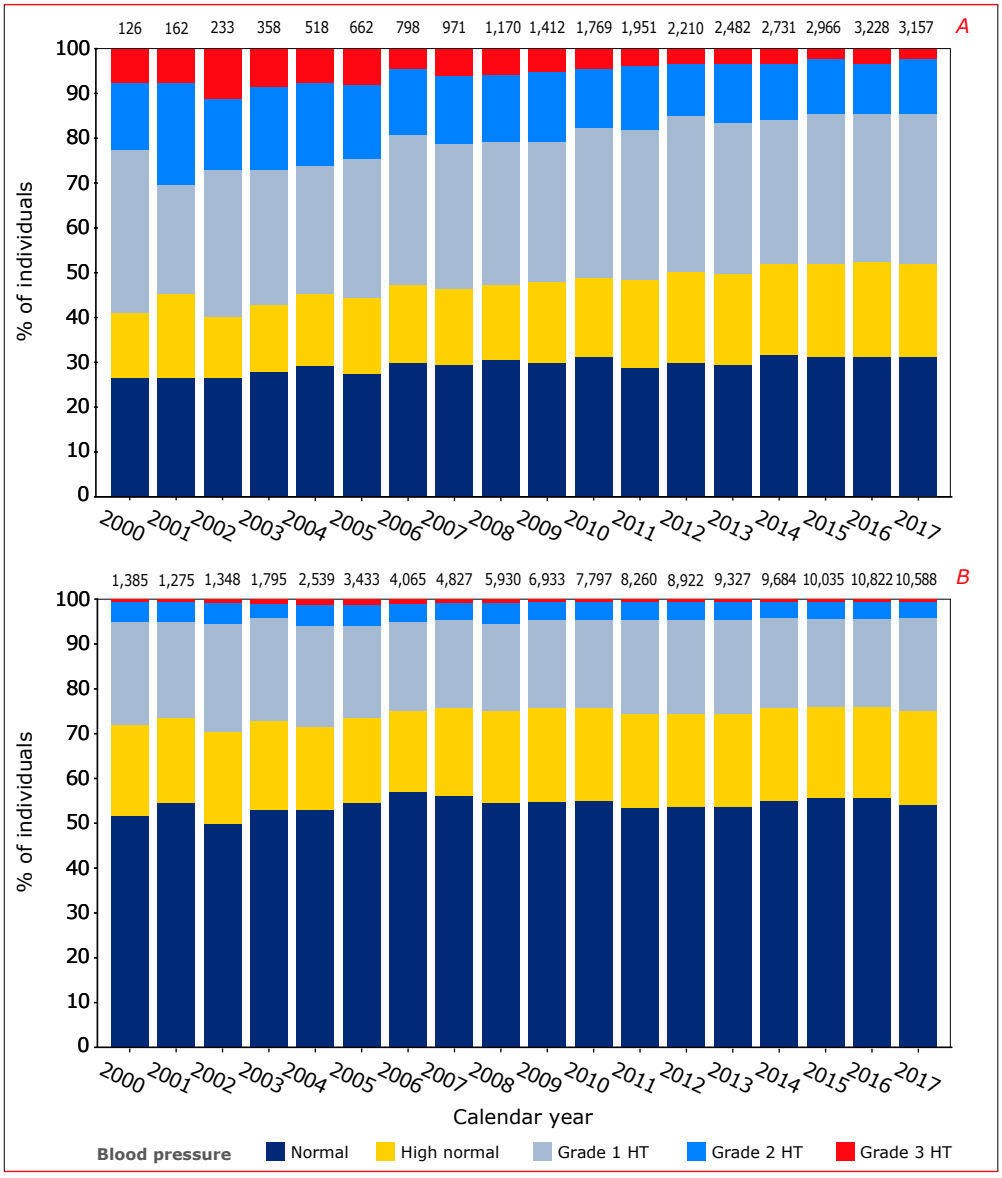
Figure 3.4: Distribution of the body mass index at the end of each calendar year in (A) men and (B) women as a percentage of the total number of men and women with a known BMI in each year. For each individual, the last available weight measurement in each year was selected. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.



Legend: BMI=body mass index.

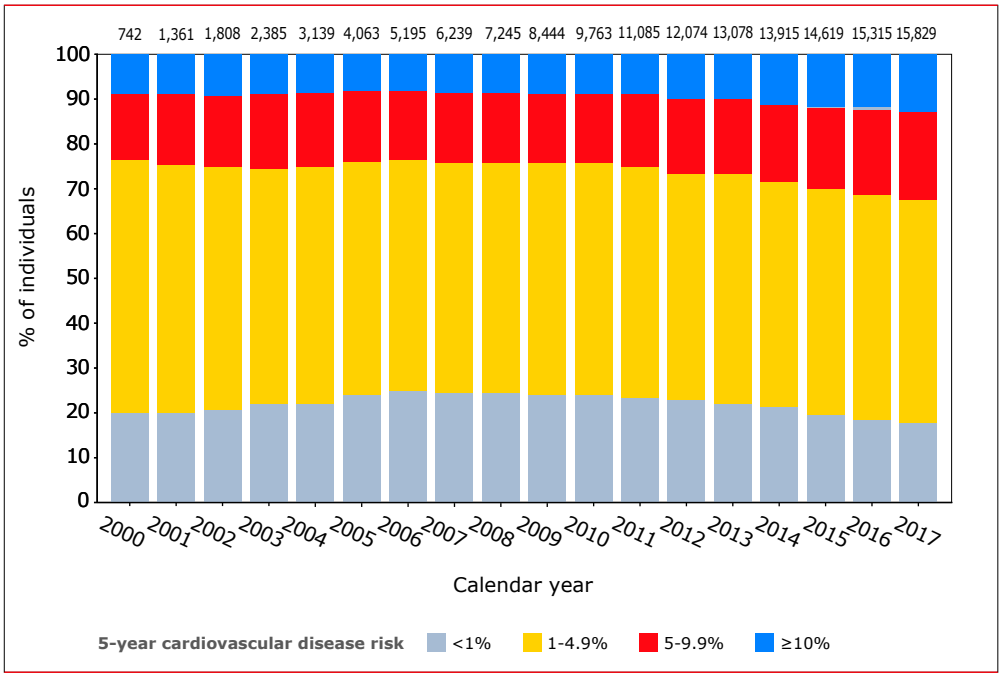
Figure 3.5A shows that, in 2017, 48% of those treated with antihypertensives still had grade 1 hypertension or higher. The figures above the bars show that, over time, an increasing number of individuals were using antihypertensives. In 2017, 2,632 (25%) individuals had grade 1-3 hypertension without specific treatment for this condition (*Figure 3.5B*). For 2,253 of these 2,632 individuals, a 5-year cardiovascular disease (CVD) risk could be calculated with the recalibrated D:A:D study algorithm[25]. Of the 2,253 individuals, 6.1% had a 5-year CVD risk of 10% or more; according to the European AIDS Clinical Society (EACS) guidelines, these individuals, in particular, should receive antihypertensive treatment[26]. *Figure 3.6* gives an overview of the cART-treated population's estimated risk of CVD over time. From 2000 until 2012, the percentage of individuals at high (5-10%) or very high (≥10%) risk remained relatively stable at around 15% and 9%, respectively, but started to increase from 2013 to 2017 to 20% and 13%, respectively. The increase in recent years in the percentage of individuals at high or very high risk may reflect the ageing of the population under study.

Figure 3.5: Distribution of graded blood pressure at the end of each calendar year in (A) individuals known to be receiving antihypertensive treatment and (B) those individuals not recorded as being treated for hypertension. For each individual, the last available systolic and diastolic blood pressure measurement in each year was selected. Blood pressure was graded according to the classification recommended in the guidelines for the management of arterial hypertension by the European Society of Hypertension and of the European Society of Cardiology[27]). 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: HT=hypertension.

Figure 3.6: Estimated five-year risk of coronary heart disease at the end of each calendar year according to the algorithm from the D:A:D: study[25]. Calculation of risk included variables such as total cholesterol, HDL cholesterol and systolic blood pressure. Values for these variables were estimated on the basis of a 'last observation carried forward' approach. An accurate assessment of an individual's risk requires recent measurements of lipid levels and blood pressure. Recent HDL cholesterol measurements were often lacking or absent. Risk could not be estimated in younger individuals in particular, because of missing data. Hence, the reported absolute number of individuals is smaller than the number of individuals in active follow up at the end of each calendar year, and older individuals are over-represented. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.



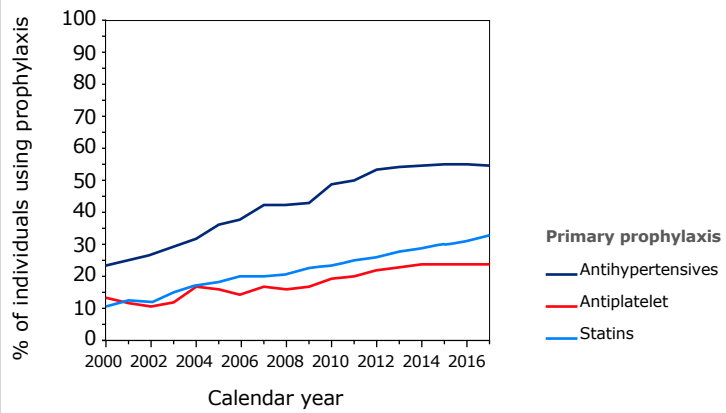
Use of primary or secondary prophylaxis for myocardial infarction or stroke

Primary prophylaxis

According to EACS guidelines, statin therapy should be offered to individuals with type 2 diabetes or a 5-year CVD risk ≥5%; angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, diuretics, and antihypertensives (verapamil or diltiazem) should be offered to individuals with a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and a 5-year CVD risk ≥10%; and acetylsalicylic acid should

be offered to individuals aged 50 years or more with a 5-year CVD risk ≥10%[28]. *Figure 3.7* shows the trends in the use of these medications in these target populations for individuals without a prior stroke, myocardial infarction, or cardiovascular surgical procedure. The percentage of individuals for whom primary prophylaxis using statins and the above-mentioned antihypertensive agents (referred to collectively hereafter as antihypertensives) is recommended has increased over time, although these percentages seem to have levelled off somewhat since 2012. Although the percentage of individuals at high risk aged 50 years or older who used acetylsalicylic acid/clopidogrel as primary prevention increased slowly up to 2012, the overall proportion remains minimal and has remained stable during the last 4 years.

Figure 3.7: *Percentage of individuals without a previous myocardial infarction, stroke, or cardiovascular surgical procedure who, according to European AIDS Clinical Society (EACS) guidelines, should be offered statin therapy, antiplatelet therapy, or antihypertensives as primary prophylaxis for myocardial infarction or stroke.*

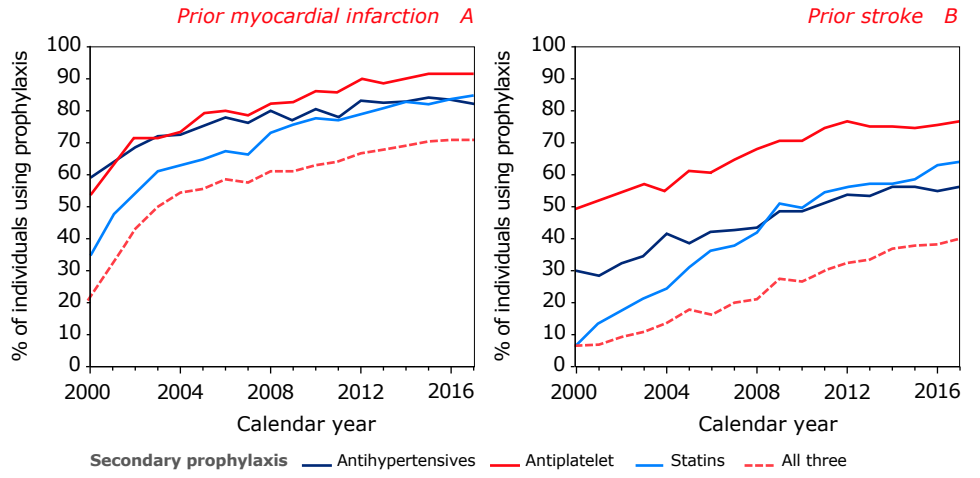


Secondary prophylaxis for myocardial infarction or stroke

According to all guidelines, individuals with a prior myocardial infarction or ischaemic stroke should receive lifelong treatment with statins, ACE inhibitors, or beta blockers or angiotensin receptor blockers (referred to here as antihypertensives), as well as low-dose acetylsalicylic acid/clopidogrel[29,30]. *Figure 3.8A* shows that the percentages of individuals using statins, acetylsalicylic acid/clopidogrel, or antihypertensives after a myocardial infarction increased between 2000 and 2017: in 2017, 85% of individuals with a prior myocardial infarction used statins, 82% used antihypertensives, and 92% used acetylsalicylic acid/clopidogrel. Although the use of statins and antihypertensives after an ischaemic stroke also

increased over time, in 2017 these medications were used less frequently after stroke than after a myocardial infarction (64% for statins, 77% for acetylsalicylic acid/clopidogrel, and 56% for antihypertensives) (*Figure 3.8B*).

Figure 3.8: *Percentage of individuals with (A) myocardial infarction or (B) ischaemic stroke using statin therapy, antiplatelet therapy, or antihypertensives.*

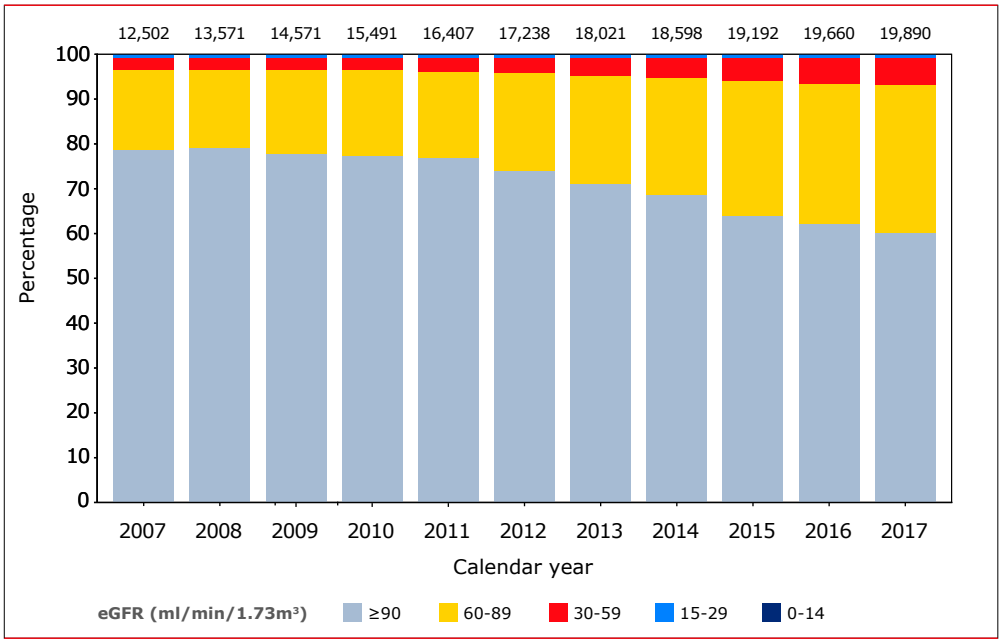


Chronic kidney disease

Glomerular filtration rate (GFR) is a marker of renal function and is commonly estimated by one of three formulae, namely, the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations[31]. As all three equations used to estimate GFR (eGFR) are based on serum creatinine, they may be markedly affected by rapid changes in muscle mass, as is seen in some individuals with advanced HIV disease who commence cART. Of these equations, both the Cockcroft-Gault and the CKD-EPI equations have been validated in HIV-positive individuals[31,32]. However, because the Cockcroft-Gault equation takes body weight into account, we have chosen to report eGFR values as estimated by this equation. The distribution of eGFR categories in ml/min/1.73m^2 (≥90, normal kidney function; 60-89, mildly reduced; 30-59, moderately reduced; 15-29, severely reduced; and <15, very severely reduced kidney function) is shown in *Figure 3.9*. The percentage of individuals with normal kidney function decreased over time from 79% in 2007 to 60% in 2017. This decrease was observed in both men and women (*Figure 3.10*). Typically, eGFR decreases with increased age, as shown in *Figure 3.11*, and therefore, the decrease in the

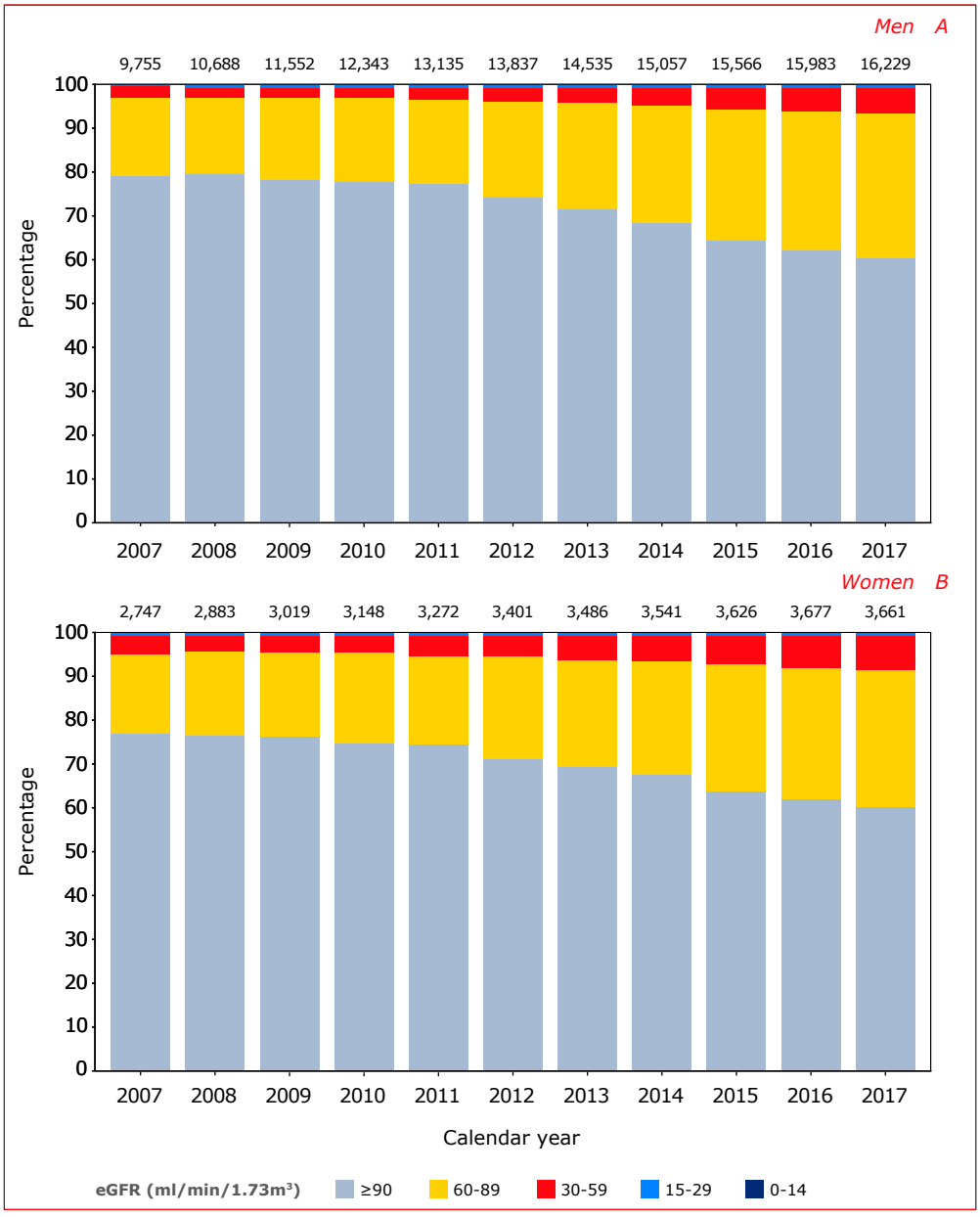
proportion of individuals with normal function over time is likely to partly reflect the increasing age of individuals in care.

Figure 3.9: Distribution of categories of estimated glomerular filtration rate (eGFR) at the end of each calendar year as a percentage of the total number of individuals with an available creatinine measurement. For each individual, the last measurement in each year was selected. The numbers at the top of each bar represent the number of individuals contributing data during that calendar year.



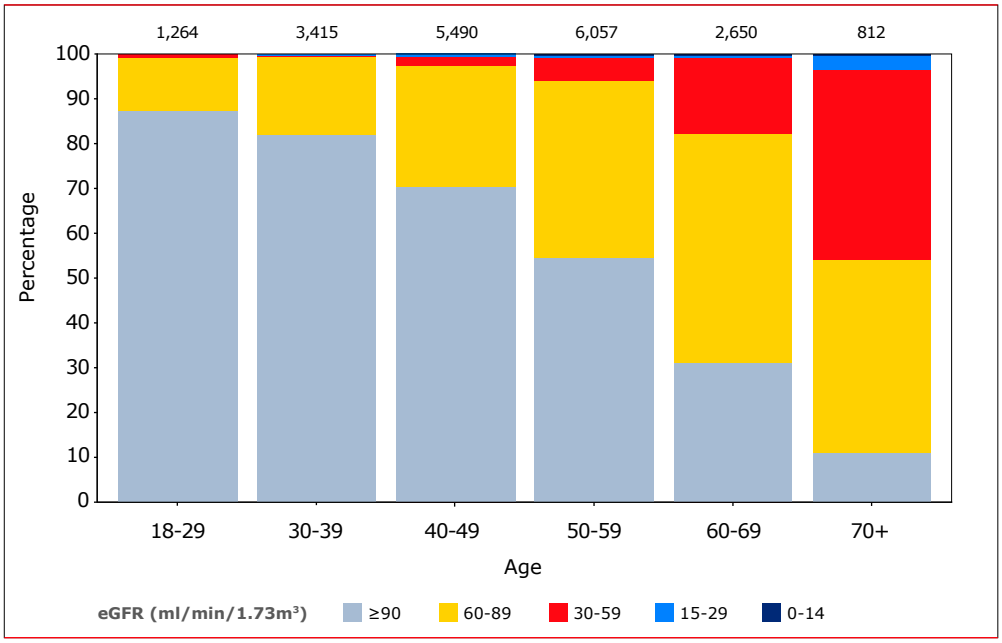
Legend: *eGFR=estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m²: normal kidney function; 60-89 ml/min/1.73m²: mildly reduced; 30-59 ml/min/1.73m²: moderately reduced; 15-29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

Figure 3.10: *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.*

Figure 3.11: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2017 for different age categories. For each individual, the last available measurement in 2017 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.*

In individuals with an eGFR >60ml/min/1.73m² at inclusion in the analyses and without previously confirmed CKD, the crude incidence of CKD, defined as eGFR <60ml/min/1.73m² confirmed by a second test at least 26 weeks later, varied over time (*Figure 3.2C*). Routine collection of serum creatinine measurements commenced in 2007. To avoid misclassifying prevalent CKD as incident CKD, we used serum creatinine levels measured in 2007 to distinguish between prevalent (CKD already present in 2007) versus new-onset incident cases of CKD (no CKD observed in 2007) from 2008 onwards. In men, the incidence rose from 7.0 cases per 1,000 PYFU in the period 2008-2010 to 10.6 in 2011-2017, and in women the incidence rose from 9.8 to 14.4 cases per 1,000 PYFU during the same periods (*Table 3.4*). The standardised incidence ratio in men, but not in women, increased significantly over time (*Table 3.4*).

Table 3.4: Crude chronic kidney disease incidence per 1,000 person years of follow up between 2008-2010 and between 2011-2016 and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Men		Women	
	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)
2008-2010	7.0 (5.8-8.4)	0.78 (0.64-0.92)	9.8 (7.1-13.2)	0.89 (0.62-1.15)
2011-2017	10.6 (9.8-11.5)	1 (reference)	14.4 (12.4-16.6)	1 (reference)

**Standardised according to the observed age distribution between 2011-2017.*

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

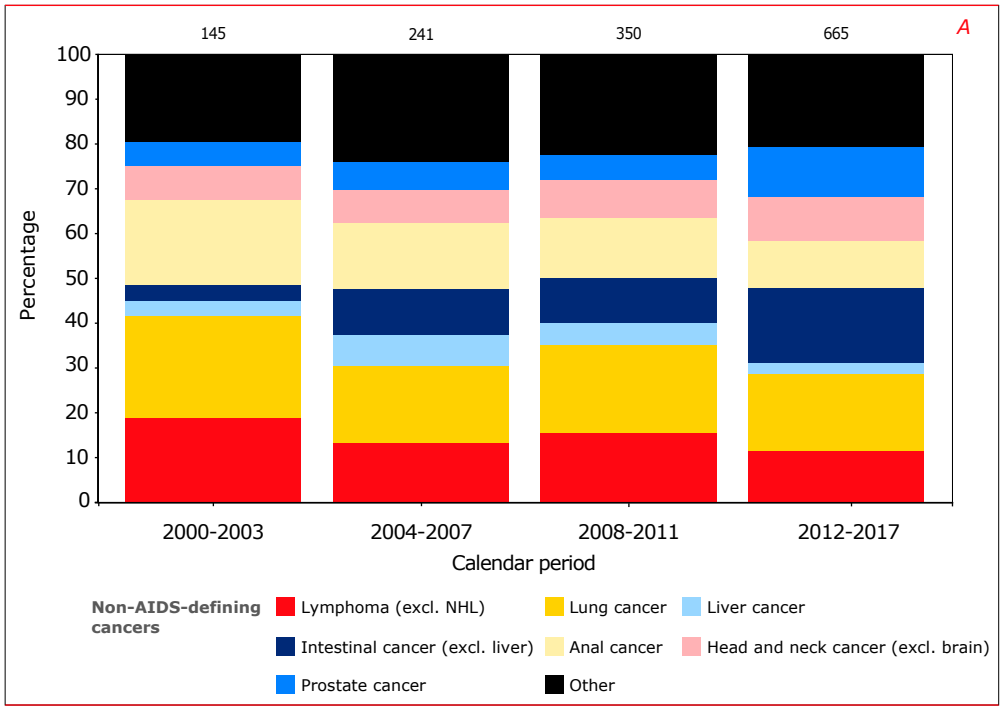
Risk factors for CKD included female gender, non-Dutch origin, low current CD4 cell count (<350 cells/mm^3), belonging to the HIV transmission risk group of people who inject drugs, older age, lower body mass index, diabetes mellitus, cardiovascular disease, being pre-treated with monotherapy and dual therapy with nucleoside analogues before the start of cART, and HBV co-infection (*Appendix Table 3.7*). When current use of cobicistat and dolutegravir were added to the model, the increased risk of CKD in the calendar period 2011-2016 disappeared in comparison to that in 2008-2010. This suggests that the increase in CKD seen in recent years is largely due to increases in serum creatinine caused by dolutegravir-induced and cobicistat-induced reversible inhibition of two transporters that mediate tubular secretion of creatinine without affecting the glomerular filtration rate, namely, organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE1).

Non-AIDS-defining malignancies

Between 2000 and 2017, 1,401 diagnoses of non-AIDS-defining malignancy in 1,307 unique individuals were recorded in SHM's database. An additional 581 patients were diagnosed with one or more non-melanoma skin cancers, but these were not included in the present analysis. *Table 3.5* shows the most common types of non-AIDS-defining cancer: lung cancer (17%), Hodgkin's lymphoma (13%), invasive anal cancer (12%), intestinal cancer (excluding liver cancer, 12%), head and neck cancers (9%), and prostate cancer (8%). *Figures 3.12A* and *B* show the relative and absolute changes in types of non-AIDS-defining cancers over time. The proportion of individuals with intestinal, prostate and renal cancer has increased over time,

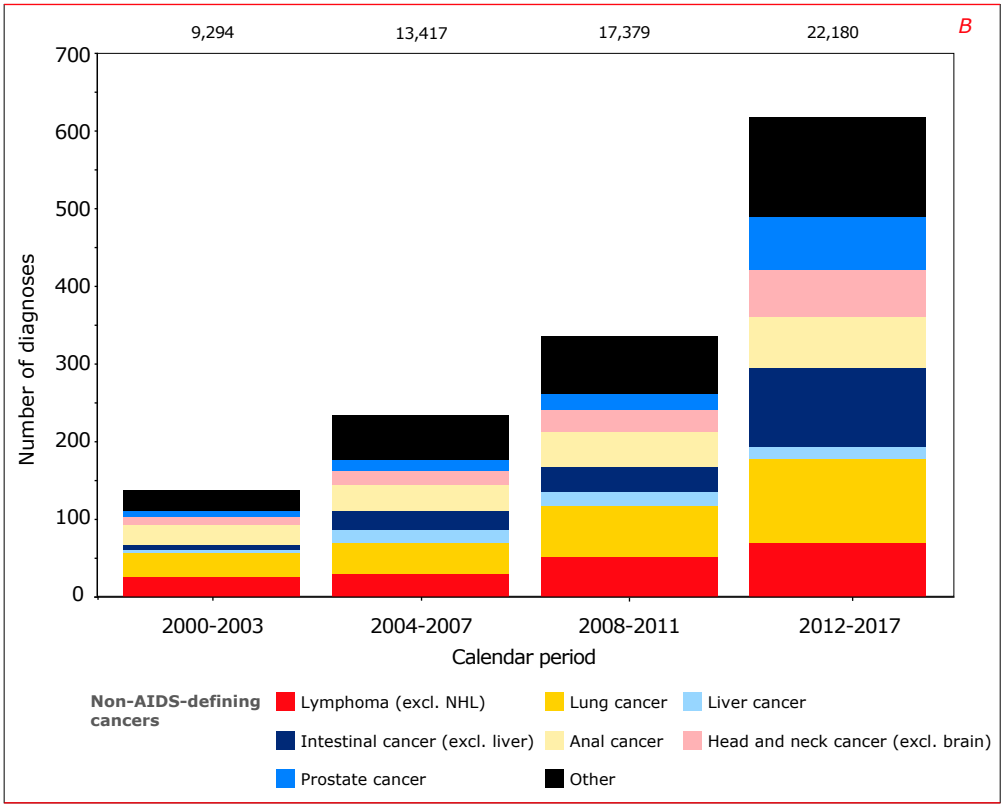
possibly reflecting the increasing age of the study population. This is further illustrated in *Figure 3.13*, which shows the distribution of non-AIDS-defining malignancies with increasing age at cancer diagnosis.

Figure 3.12A: *Relative changes in non-AIDS-defining malignancies between 2000 and 2017 in HIV-1-positive individuals in the Netherlands. The numbers at the top of each bar represent the number of non-AIDS-defining cancer diagnoses during that calendar period.*



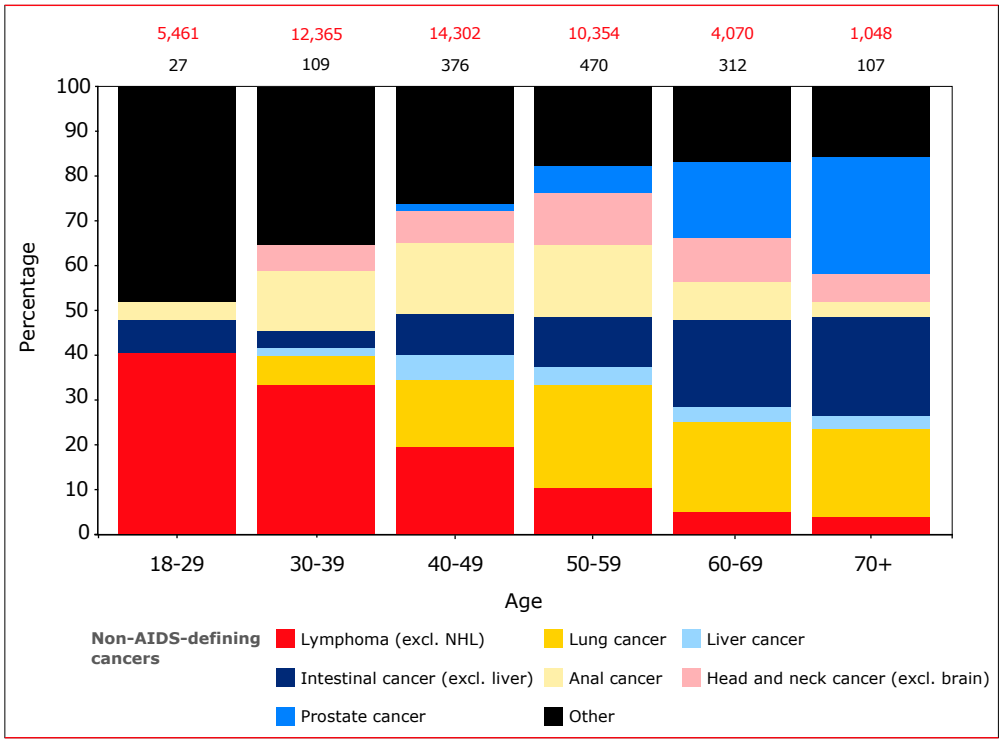
Legend: *excl.=excluding; NHL=non-Hodgkin's lymphoma.*

Figure 3.12B: Absolute number of non-AIDS-defining malignancies between 2000 and 2017 in HIV-1-positive individuals in the Netherlands. The numbers at the top of each bar represent the number of individuals at risk during that calendar period.



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

Figure 3.13: Relative changes in non-AIDS-defining malignancies with increasing age in HIV-1-positive individuals in the Netherlands. The numbers at the top of each bar represent the number of individuals at risk and the number of cancer diagnoses in that age category between 2000 and 2017.



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

The crude incidence of non-AIDS-defining malignancies in men increased slightly from 6.0 cases per 1,000 PYFU in 2000-2005 to 6.7 cases per 1,000 PYFU in 2011-2017, and in women from 2.0 in 2000-2005 to 4.0 cases per 1,000 PYFU in 2011-2017 (*Figure 3.2D*; *Appendix Table 3.6D*). However, when the changes in the age distribution of the HIV-positive population were taken into account, the age-standardised incidence in men was actually lower in the period 2011-2017 than in 2000-2005 and 2006-2010 (*Table 3.6*). This lower standardised incidence in men may be due to changes over time in risk factors such as smoking and a higher proportion of individuals living with high CD4 cell counts. In women, the age-standardised incidence was lower in the period 2011-2017 than in 2006-2010, but not 2000-2005.

Table 3.5: Most common non-AIDS-defining malignancies diagnosed between 2000-2017.

Non-AIDS-defining malignancy	Number of malignancies	%	5-year survival
Lung cancer	242	17.3	11.5
Lymphoma (excluding non-Hodgkin's lymphoma)	182	13.0	66.9
Anal cancer	169	12.1	63.2
Intestinal cancer (excluding liver)	166	11.8	31.4
Head and neck cancer (excluding brain)	120	8.6	57.9
Prostate cancer	107	7.6	78.5
Other cancers	89	6.4	48.5
Renal and bladder cancer	74	5.3	63.5
Malignant melanoma	56	4.0	67.4
Liver cancer	54	3.9	11.3
Leukaemia	42	3.0	40.8
Breast cancer	35	2.5	81.8
Testicular cancer	26	1.9	87.7
Gynaecological cancer (excluding cervical)	21	1.5	61.7
CNS cancer	18	1.3	28.9

Table 3.6: Crude non-AIDS-defining malignancy incidence per 1,000 person years of follow up between 2000-2005, 2006-2010, and 2011-2017, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Men		Women	
	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)	Incidence/1000 PYFU (95% CI)	Standardised incidence ratio* (95% CI)
2000-2005	6.0 (5.2-6.8)	1.35 (1.17-1.52)	2.0 (1.2-3.1)	0.85 (0.47-1.24)
2006-2010	7.1 (6.4-7.9)	1.33 (1.19-1.47)	4.0 (3.0-5.3)	1.39 (1.01-1.76)
2011-2017	6.7 (6.2-7.2)	1 (reference)	4.0 (3.2-4.9)	1 (reference)

**Standardised according to the observed age distribution between 2011-2017.*

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

Demographic and clinical factors significantly associated with an increased risk of a first non-AIDS-defining malignancy were older age, having acquired HIV-1 through injecting drugs or contact with blood or blood products, lower current CD4 cell count (CD4 below 350 cells/mm^3), low body mass index, prior AIDS, chronic HBV co-infection, and current and/or past smoking (*Appendix Table 3.7*).

In the period from 1 January 2000 to 31 December 2017, the 5-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma

skin cancers and invasive anal cancers) was 47.3%, compared with 69.6% for CVD, 81.0% for DM, and 83.9% for CKD (*Appendix Figure 3.2*). In the same period, the 5-year survival rate of adults newly-entering care in one of the Dutch HIV treatment centres was 95.4%, and 82.2% for those newly entering care with an AIDS diagnosis. The 5-year survival rates following the most common non-AIDS-defining malignancies are shown in *Table 3.5* and *Appendix Figure 3.3*.

Anal cancer

In total, 3 HIV-positive women and 166 HIV-positive men were diagnosed with anal cancer. Among HIV-positive men, the incidence of anal cancer slowly decreased over time from 0.7 cases per 1,000 PYFU in 2000 to 0.2 cases per 1,000 PYFU in 2017 (*Figure 3.2G*). This decreasing trend in the incidence of anal cancer might be due to the trend over calendar time to start cART at higher CD4 counts, as both a lower nadir CD4 cell count and lower current CD4 cell count have each been associated with an increased risk of anal cancer[33]. Furthermore, screening for both anal cancer (and pre-cancerous stages of anal cancer) and treatment of anal intraepithelial neoplasia may also have contributed to the decrease in anal cancer. A 2015 study exploring the incidence of anal cancer among HIV-1-positive individuals in the Netherlands showed a significantly higher incidence of anal cancer in men who have sex with men (MSM) than in heterosexual men[34]. However, in this chapter, we will not report on the trend in anal cancer among heterosexual men over time, as the number of heterosexual men with anal cancer is too small (n=14) to observe a decreasing trend in anal cancer in this group.

Immunological non-response and risk of disease progression and death three years after starting cART

Of 6,124 therapy-naive individuals who started cART with less than 350 CD4 cells/mm^3 since 1996 and who had experienced at least 3 years of viral suppression on cART, 1,325 were classified as immunological non-responders (defined as having less than 350 CD4 cells/mm^3 after 3 years of viral suppression on cART) and 4,799 individuals were defined as having a good immunological response (a CD4 cell count of 350 cells/mm^3 or higher after 3 years of viral suppression on cART). We analysed the association between immunological response/non-response and the risk of the following endpoints: death, AIDS, non-AIDS-defining malignancy, diabetes mellitus, and cardiovascular disease. We considered only first events and excluded those individuals in whom a particular endpoint had already occurred prior to the start of the observation for this analysis (these were mainly prior AIDS events). Changes in immune status and/or plasma viraemia and/or use of cART after the initial 3 years of cART were ignored in this analysis – individuals remained in their original category of immunological responder/non-responder. The number

of events, crude incidence per 1,000 PYFU, and age-standardised incidence ratio of these events are reported in *Table 3.7*. Although the crude incidences of death, AIDS, non-AIDS-defining malignancies and cardiovascular disease were higher in the immunological non-responders, the age-standardised incidence ratio only reached statistical significance for death and came close to reaching statistical significance for cardiovascular disease and non-AIDS-defining malignancy. After further adjustment for current age, region of origin, gender, and HBV and HCV status, immunological non-response remained significantly associated with death (relative risk [RR] 1.38, 95% CI 1.09-1.75, p=0.009), but not with non-AIDS-defining malignancy (RR 1.28, 95% CI 0.95-1.73, p=0.11), AIDS (RR 1.20, 95% CI 0.76-1.91, p=0.43), diabetes mellitus (RR 0.80, 95% CI 0.57-1.13, p=0.20), or cardiovascular disease (RR 1.27, 95% CI 0.96-1.70, p=0.10). However, as the number of endpoints are small, these results should be interpreted with caution.

Table 3.7: *Crude incidence per 1,000 person years of follow up and age-standardised incidence ratio with 95% confidence intervals of various clinical endpoints. The study population consists of individuals who started cART with a CD4 cell count below 350 cells/mm³ and after 3 years of virologically successful cART were either immunological responders (CD4 cell count ≥ 350 cells/mm³) or non-responders (CD4 cell count < 350 cells/mm³).*

Outcome	**Crude rate**			**Standardised rate***	
Immune response	Person years	Number of endpoints	Rate/1,000 PY (95% CI)	SIR (95% CI)	p-value
Death					
Responder (CD4 ≥350)	34,561	203	5.87 (5.09-6.74)	1 (reference)	.
Non-responder (CD4 <350)	10,458	108	10.33 (8.47-12.47)	1.34 (1.09-1.59)	0.009
AIDS					
Responder (CD4 ≥350)	26,074	83	3.18 (2.54-3.95)	1 (reference)	.
Non-responder (CD4 <350)	5,738	24	4.18 (2.68-6.22)	1.18 (0.71-1.66)	0.448
Non-AIDS-defining malignancy					
Responder (CD4 ≥350)	33,841	133	3.93 (3.29-4.66)	1 (reference)	.
Non-responder (CD4 <350)	10,169	64	6.29 (4.85-8.04)	1.27 (0.96-1.59)	0.085
Diabetes mellitus					
Responder (CD4 ≥350)	32,892	149	4.53 (3.83-5.32)	1 (reference)	.
Non-responder (CD4 <350)	9,928	43	4.33 (3.13-5.83)	0.82 (0.58-1.07)	0.160
Cardiovascular disease					
Responder (CD4 ≥350)	33,954	147	4.33 (3.66-5.09)	1 (reference)	.
Non-responder (CD4 <350)	10,128	71	7.01 (5.47-8.84)	1.27 (0.97-1.56)	0.076

**Standardised according to the observed age distribution in the immunological responders.*

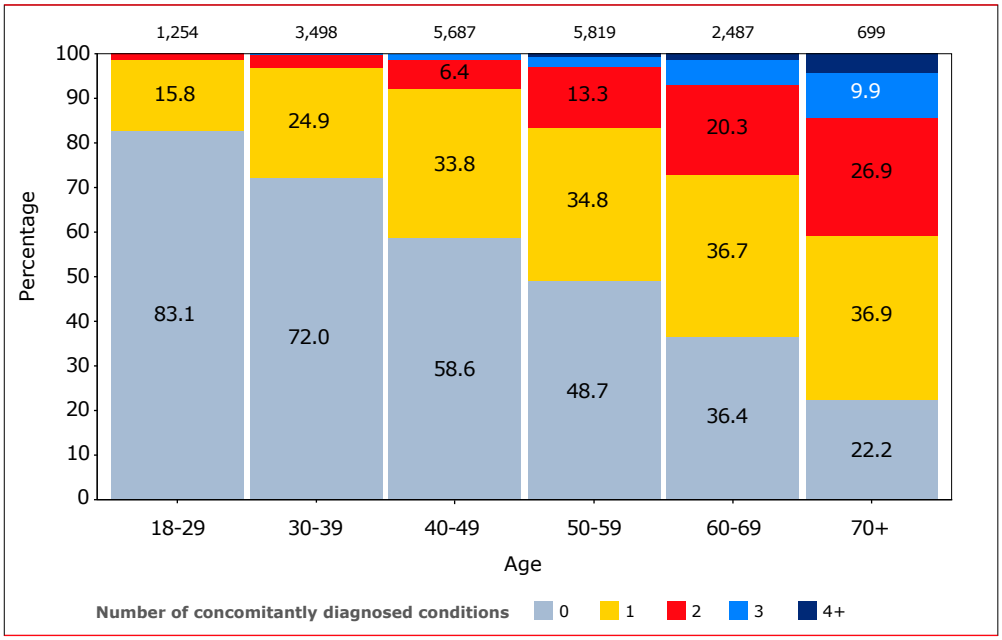
Legend: *SIR=standardised incidence ratio; 95% CI=95% confidence interval; PY=person years.*

Multimorbidity

We investigated changes over time in the prevalence of non-AIDS multimorbidity. HIV infection itself and AIDS diagnoses did not contribute to the multimorbidity score. 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; (6) hypertension, defined as the use of antihypertensive drugs and/or a measured grade 2 (or higher) hypertension with systolic pressure ≥160 mmHg and/or diastolic pressure ≥100 mmHg; (7) obesity (BMI over 30). Note that more stringent definitions of CKD and hypertension have been applied here than in the analyses presented earlier in this chapter so as to avoid overdiagnosis of both CKD in people using antiretroviral drugs that inhibit tubular secretion of creatinine and hypertension in those with borderline hypertension. Recurrences and second events of CVD, stroke, and non-AIDS-defining malignancies were not considered. Finally, CKD, hypertension and obesity could be reversible.

Figure 3.14 shows the distribution of the number of concomitantly diagnosed conditions in various age categories of the adult population in 2017. The number of concomitant conditions was slightly higher in women than in men for all age categories (*Appendix Figure 3.4*). Moreover, although the average number of concomitant conditions has steadily increased over the past 10 years because of the increasing average age of the cohort, the prevalence of multimorbidity by age category has remained stable over the same period (*Appendix Figure 3.5*).

Figure 3.14: Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2017. 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.



Summary and conclusions

AIDS, mortality and causes of death

AIDS-related deaths have decreased dramatically since cART became available in the Netherlands in 1996, consistent with reductions reported in studies from Spain[35], Denmark[36], several other European countries[37], and the USA[38]. The limited, but decreasing, number of individuals who still die of AIDS each year consists mainly of those presenting late for care with already advanced immunodeficiency. Nonetheless, overall, the 5-year survival after a first AIDS-defining condition was far greater than after a diagnosis of cardiovascular disease (CVD) or a non-AIDS-defining malignancy. Death is increasingly likely to be the result of a non-AIDS cause, with CVD and non-AIDS malignancies being the most common. This not only reflects the increased risk of non-AIDS morbidity in individuals with more advanced HIV infection, but also the continuously increasing age of the population of individuals in care. As a result, on average, mortality rates among people living

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

Diabetes and cardiovascular disease

Whereas the crude incidence of diabetes mellitus and CVD in men and women was found to have remained relatively stable, the age-standardised incidence for both diseases declined over time in men. The decline in age-standardised incidence in men may suggest improved awareness, prevention (including switching from drugs associated with an increased risk of diabetes mellitus[41] and myocardial infarction[42,43] to those that, to date, have not been associated with such risks), and increased attention to managing traditional risk factors for these conditions. Furthermore, the declining trend of age-standardised incidence may also reflect an increasing proportion of individuals with high CD4 cell counts (partly because of the trend over time to start cART at higher CD4 cell counts, but also because an increasing proportion of individuals have been using cART long enough to have reached high CD4 cell counts). The observation that the age-standardised incidence ratios do not decline as much in women remains unexplained and needs further study. Finally, risk factors were mainly those traditionally known to be associated with diabetes mellitus and CVD (including age, hypertension, smoking and obesity), similar to those previously reported in other studies[41,44,45]. Several of these risk factors have been reported to be more prevalent among people living with HIV[19].

Cardiovascular risk factors

Despite the increasing age of the HIV-positive population, the proportion at high or very high cardiovascular risk increased only slightly over the period 2000-2017. This suggests that cardiovascular risk management has improved over time, as illustrated by the increasing use of statins and antihypertensives over time and the shift away from the use of antiretrovirals that have been demonstrated to be associated with increased cardiovascular risk, particularly in individuals with high underlying risk[46] (*Chapter 2*). Significant room for further improvement remains, however, given the suboptimal use of statin therapy, antihypertensive therapy, and low-dose acetylsalicylic acid as secondary prevention following a myocardial infarction or ischaemic stroke, and the low, albeit slowly improving, uptake of these medications in the prevention of primary cardiovascular disease.

The clinical significance of the increase in BMI over time, especially in women, requires further study. Recent results have suggested that weight gain after starting cART is associated with lower mortality for normal-weight individuals,

but found no clear benefit for overweight or obese individuals[47]. However, another study found that weight gain after starting cART was associated with an increased risk of diabetes, and, in those with a pre-antiretroviral therapy BMI in the normal range, with an increased risk of cardiovascular disease[48]. Prospective longitudinal monitoring of lipid levels, smoking status, blood pressure, weight, and other risk factors will be important to further optimise the assessment of cardiovascular risk in our increasingly ageing HIV-1-positive population and to study the impact of interventions, such as the use of statins and antihypertensive therapy, in modifying disease risk.

Renal insufficiency

Since 2008, there has been a steady increase in the incidence of new-onset chronic kidney disease (CKD). As expected, older individuals and those with traditional risk factors such as older age and hypertension were found to be at increased risk for CKD, as were individuals with advanced immunodeficiency. In addition, other studies have reported hepatitis B and C virus co-infection[49,50] and the use of tenofovir disoproxil fumarate, atazanavir/ritonavir, and lopinavir/ritonavir to be additional independent predictors of chronic renal impairment[51]. Renal impairment in the HIV-positive population is associated with an increased risk for cardiovascular disease[52]. The increase in 'CKD' in recent years appears to be at least partially caused by the increased use of dolutegravir and cobicistat, both 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 in the Netherlands are lung, anal, and head and neck cancer, as well as Hodgkin's lymphoma. The crude incidence of non-AIDS-defining malignancies in the Netherlands has remained stable over time, and we also observed a decline in age-standardised incidence of non-AIDS-defining malignancies in men. In addition, our analyses show that individuals diagnosed with non-AIDS-defining malignancies were more likely to be older. This is in line with data from other cohorts, including the Swiss HIV cohort, that have also reported an increased incidence of non-AIDS-defining malignancies with increasing age[53,54,55,56]. Our analyses also showed that individuals diagnosed with non-AIDS-defining malignancies were more likely to be current or past smokers and more likely to have lower CD4 counts (the effect was significant with CD4 cell counts below 350 cells/mm^3) and a prior AIDS diagnosis. Other studies reported that the effect of immunodeficiency may be stronger for infection-related non-AIDS-defining malignancies[57]. The 5-year survival rate after

a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 47.3%.

Our analyses found no association between duration of cART and the incidence of non-AIDS-defining malignancies. On the other hand, a 2015 paper from the D:A:D study looking at the association between non-AIDS-defining malignancies and cumulative cART use in a large study population, revealed an overall increase in the risk of non-AIDS-defining malignancies with longer exposure to a protease inhibitor-based cART regimen. This association was observed particularly for anal cance[58]. As we did not examine individual cART regimens, no conclusion can as yet be drawn from the D:A:D study in terms of the situation in the Netherlands.

Recommendations

Although the proportion of individuals dying of AIDS in the Netherlands has markedly declined throughout the cART era, further improvement can be made by identifying individuals at earlier stages of infection, with immediate linkage to care to allow timely initiation of treatment. It is to be expected that this may also have a beneficial impact on the incidence of those comorbidities, such as non-AIDS-defining malignancies, for which advanced immunodeficiency is a contributing risk factor[59,60,61]. In addition, screening for pre-cancerous stages of anal cancer and prevention, identification, and appropriate treatment of viral hepatitis co-infections may also contribute to reducing the incidence of such comorbidities.

The relatively poor 5-year survival rates following the diagnosis of several of the analysed non-AIDS-defining comorbidities compared to survival of patients newly entering care with an AIDS diagnosis underlines the importance of primary prevention, early diagnosis and aggressive pursuit of secondary prevention and treatment of non-AIDS comorbidities in the HIV-positive population. Studies such as the ongoing Comorbidity and Aging with HIV (AGEhIV) cohort study are needed to provide further insights into the independent contribution of HIV and HIV-associated factors, such as innate and adaptive immune and coagulation activation and inflammation, which will hopefully guide the development of interventions that target relevant pathophysiological mechanisms[9,62].

It is important to note that the risk of many, if not each, of the comorbidities frequently identified in people living with HIV is determined by multiple factors. Besides immunodeficiency, additional key contributors for consideration include both well-known traditional unmodifiable risk factors, such as age and genetic

predisposition, and modifiable lifestyle-related factors, as well as known, and perhaps as yet unknown, effects of antiretroviral treatment and co-infection. Development of antiretroviral agents with improved safety profiles for long-term use should continue to remain a priority, given the association of some of the current generation of drugs with CKD, cardiovascular outcomes, bone density loss, and possibly cancer[63].

Ageing, of course, strongly contributes to the risk of the development of comorbidity, ranging from cardiovascular and chronic kidney disease to diabetes mellitus and non-AIDS malignancies. Given the steadily rising average age of individuals with HIV, it will be imperative to ensure the continued collection of high quality information regarding comorbidities and their risk factors.

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

References

1. van Sighem, A. I. *et al.* Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. *AIDS* **24,** 1527–35 (2010).
2. Mocroft, A. *et al.* AIDS across Europe, 1994-98: the EuroSIDA study. *Lancet* **356,** 291–6 (2000).
3. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* **372,** 293–299 (2008).
4. Emery, S. *et al.* Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. *J. Infect. Dis.* **197,** 1133–1144 (2008).
5. Mocroft, A. *et al.* Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? *AIDS* **19,** 2117–25 (2005).
6. Bhaskaran, K. *et al.* Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA* **300,** 51–9 (2008).
7. Lohse, N. *et al.* Survival of persons with and without HIV infection in Denmark, 1995-2005. *Ann. Intern. Med.* **146,** 87–95 (2007).
8. Bonnet, F. *et al.* Changes in cancer mortality among HIV-infected patients: the Mortalité 2005 Survey. *Clin. Infect. Dis.* **48,** 633–9 (2009).
9. Guaraldi, G. *et al.* Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin. Infect. Dis.* **53,** 1120–1126 (2011).
10. Freiberg, M. S. *et al.* The risk of incident coronary heart disease among veterans with and without HIV and hepatitis C. *Circ. Cardiovasc. Qual. Outcomes* **4,** 425–32 (2011).
11. Schouten, J. *et al.* Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between hiv-infected and uninfected individuals: the AGE_hIV cohort study. *Clin. Infect. Dis.* **59,** 1787–1797 (2014).
12. Hsue, P. Y. *et al.* Role of HIV and human herpesvirus-8 infection in pulmonary arterial hypertension. *AIDS* **22,** 825–33 (2008).
13. Arnsten, J. H. *et al.* Decreased bone mineral density and increased fracture risk in aging men with or at risk for HIV infection. *AIDS* **21,** 617–623 (2007).
14. Brown, T. T. & Qaqish, R. B. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* **20,** 2165–2174 (2006).
15. Triant, V. A., Brown, T. T., Lee, H. & Grinspoon, S. K. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. *J. Clin. Endocrinol. Metab.* **93,** 3499–3504 (2008).

16. McCutchan, J. A. *et al.* HIV suppression by HAART preserves cognitive function in advanced, immune-reconstituted AIDS patients. *AIDS* **21,** 1109–17 (2007).
17. Robertson, K. R. *et al.* The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS* **21,** 1915–21 (2007).
18. Ances, B. M. *et al.* HIV infection and aging independently affect brain function as measured by functional magnetic resonance imaging. *J. Infect. Dis.* **201,** 336–340 (2010).
19. Clifford, G. M. *et al.* Cancer risk in the Swiss HIV cohort study: Associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J. Natl. Cancer Inst.* **97,** 425–432 (2005).
20. Grulich, A. E., van Leeuwen, M. T., Falster, M. O. & Vajdic, C. M. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* **370,** 59–67 (2007).
21. Baker, J. V *et al.* CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS* **22,** 841–848 (2008).
22. El-Sadr, W. M. *et al.* CD4+ count-guided interruption of antiretroviral treatment. *N. Engl. J. Med.* **355,** 2283–96 (2006).
23. CDC Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report, 2005.* **Vol. 17. R,** (U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2007).
24. Tripepi, G., Jager, K. J., Dekker, F. W. & Zoccali, C. Stratification for confounding-part 2: direct and indirect standardization. *Nephron Clin.Pract.* **116,** c322–c325 (2010).
25. Friis-Møller, N. *et al.* An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. *Eur. J. Prev. Cardiol.* **23,** 214–23 (2016).
26. European AIDS Clinical Society. Guidelines. Version 8.0, October 2015. English edition. (2015).
27. Mancia, G. *et al.* 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur. Heart J.* **34,** 2159–2219 (2013).
28. Rockstroh, J. K. *et al.* European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. *HIV Med.* **9,** 82–88 (2008).
29. Nederlands Huisartsen Genootschap. Beroerte (2015). Available at: *https://www.nhg.org/standaarden/samenvatting/beroerte*
30. Nederlands Huisartsen Genootschap Cardiovasculair Risicomanagement. (2016). Available at: *https://www.nhg.org/standaarden/samenvatting/cardiovasculair-risicomanagement.*

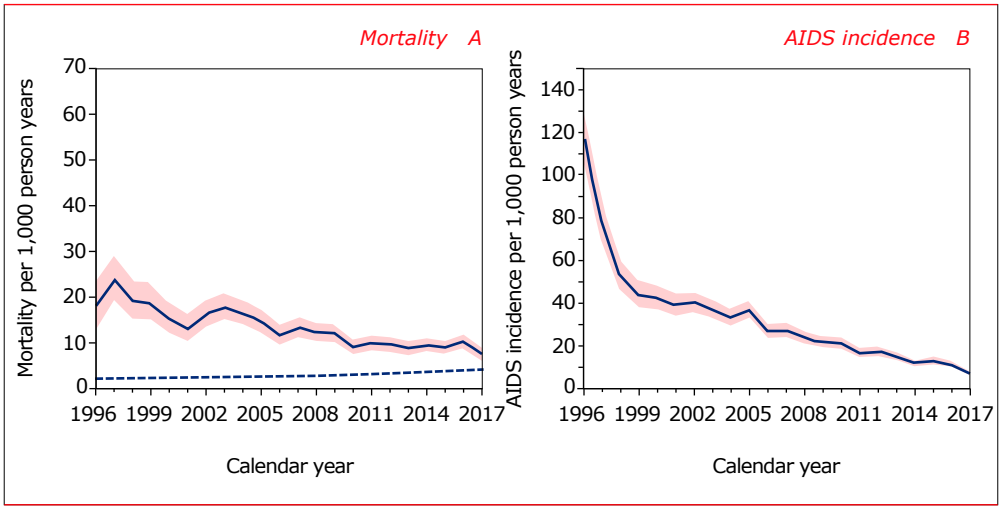
31. Mocroft, A. *et al.* A comparison of estimated glomerular filtration rates using cockcroft-gault and the chronic kidney disease epidemiology collaboration estimating equations in HIV infection. *HIV Med.* **15,** 144–152 (2014).
32. Vrouenraets, S. M. *et al.* A comparison of measured and estimated glomerular filtration rate in successfully treated HIV-patients with preserved renal function. *Clin.Nephrol.* **77,** 311–320 (2012).
33. De Pokomandy, A. *et al.* HAART and progression to high-grade anal intraepithelial neoplasia in men who have sex with men and are infected with HIV. *Clin. Infect. Dis.* **52,** 1174–1181 (2011).
34. Richel, O. *et al.* Anal Cancer in the HIV-Positive Population: Slowly Declining Incidence After a Decade of cART. *J. Acquir. Immune Defic. Syndr.* **69,** 602–605 (2015).
35. Berenguer, J. *et al.* Trends in mortality according to hepatitis C virus serostatus in the era of combination antiretroviral therapy. *AIDS* **26,** 2241–6 (2012).
36. Helleberg, M. *et al.* Causes of death among Danish HIV patients compared with population controls in the period 1995-2008. *Infection* **40,** 627–634 (2012).
37. Mocroft, A. *et al.* Decline in the AIDS and death rates in the EuroSIDA study: An observational study. *Lancet* **362,** 22–29 (2003).
38. Holtgrave, D. R. Causes of the decline in AIDS deaths, United States, 1995-2002: prevention, treatment or both? *Int. J. STD AIDS* **16,** 777–781 (2005).
39. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord *et al.* All-cause mortality in treated HIV-infected adults with CD4 ≥500/mm^3 compared with the general population: evidence from a large European observational cohort collaboration. *Int. J. Epidemiol.* **41,** 433–45 (2012).
40. May, M. T. *et al.* Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. *AIDS* **28,** 1193–1202 (2014).
41. Capeau, J. *et al.* Ten-year diabetes incidence in 1046 HIV-infected patients started on a combination antiretroviral treatment. *AIDS* **26,** 303–14 (2012).
42. Worm, S. W. *et al.* High prevalence of the metabolic syndrome in HIV-infected patients: impact of different definitions of the metabolic syndrome. *AIDS* **24,** 427–435 (2010).
43. Sabin, C. A. *et al.* Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration. *BMC Med.* **14,** 61 (2016).
44. Ledergerber, B. *et al.* Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. *Clin Infect Dis* **45,** 111–119 (2007).

45. Brown, T. T. T. *et al.* Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch. Intern. Med.* **165,** 1179–84 (2005).
46. Kamara, D. A. *et al.* Longitudinal analysis of the associations between antiretroviral therapy, viraemia and immunosuppression with lipid levels: the D:A:D study. *Antivir. Ther.* (2016). doi:10.3851/IMP3051
47. Yuh, B. *et al.* Weight change after antiretroviral therapy and mortality. *Clin. Infect. Dis.* **60,** 1852–1859 (2015).
48. Achhra, A. C. *et al.* Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. *HIV Med.* **17,** 255–68 (2016).
49. Mocroft, A. *et al.* Hepatitis B and C co-infection are independent predictors of progressive kidney disease in hiv-positive, antiretroviral-treated adults. *PLoS One* **7,** e40245 (2012).
50. Peters, L. *et al.* Hepatitis C virus viremia increases the incidence of chronic kidney disease in HIV-infected patients. *AIDS* **26,** 1917–1926 (2012).
51. Ryom, L. *et al.* Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: The D:A:D Study. *J. Infect. Dis.* **207,** 1359–1369 (2013).
52. Ryom, L. *et al.* Renal impairment and cardiovascular disease in HIV-positive individuals; The D:A:D Study. *J. Infect. Dis.* **214,** 1212–20 (2016).
53. Krishnan, S. *et al.* Incidence of Non-AIDS-defining cancer in antiretroviral treatment-naïve subjects after antiretroviral treatment initiation: An ACTG longitudinal linked randomized trials analysis. *Oncology* **80,** 42–49 (2011).
54. Powles, T. *et al.* Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection. *J. Clin. Oncol.* **27,** 884–890 (2009).
55. Sigel, K. *et al.* HIV as an independent risk factor for incident lung cancer. *AIDS* **26,** 1017–25 (2012).
56. Hasse, B. *et al.* Morbidity and aging in HIV-infected persons: The swiss HIV cohort study. *Clin. Infect. Dis.* **53,** 1130–1139 (2011).
57. Kesselring A, Gras L, Smit C. *et al.* Immunodeficiency as a risk factor for non-AIDS-defining malignancies in HIV-1-infected patients receiving combination antiretroviral therapy. *Clin. Infect. Dis.* **52,** 1458–1465 (2011).
58. Bruyand, M. *et al.* Cancer risk and use of protease inhibitor or nonnucleoside reverse transcriptase inhibitor-based combination antiretroviral therapy: the D: A: D study. *J. Acquir. Immune Defic. Syndr.* **68,** 568–77 (2015).
59. Grinsztejn, B. *et al.* Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: Results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect. Dis.* **14,** 281–290 (2014).

60. The TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N. Engl. J. Med.* **373,** 808–22 (2015).
61. Lundgren, J. D. *et al.* Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N. Engl. J. Med.* **373,** 795–807 (2015).
62. High, K. P. *et al.* HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. *J. Acquir. Immune Defic. Syndr.* **60 Suppl 1,** S1-18 (2012).
63. Chao, C. *et al.* Exposure to antiretroviral therapy and risk of cancer in HIV-infected persons. *AIDS* **26,** 2223–31 (2012).

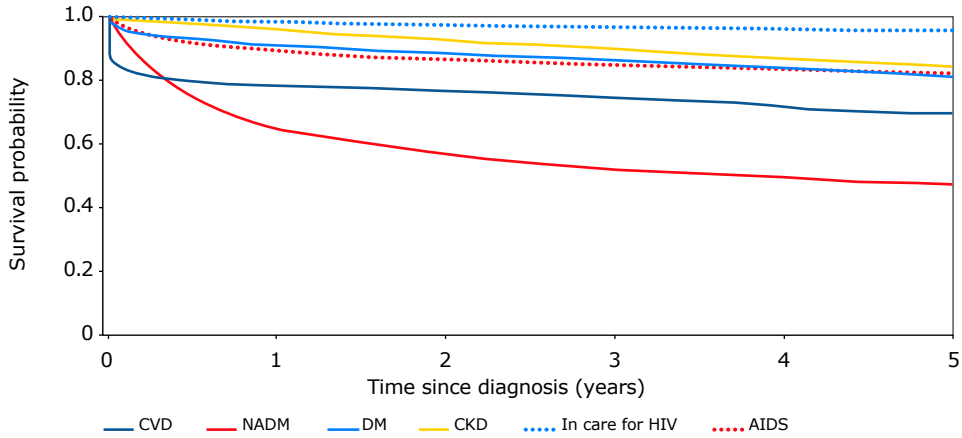
Appendix: supplementary figures and tables

Appendix Figure 3.1: *(A) Annual mortality and (B) incidence of AIDS in 25,524 HIV-1-positive individuals in the Netherlands after HIV diagnosis from 1996 onwards. Solid lines represent the incidence, while the shaded areas are the 95% confidence intervals. The dashed line is the mortality rate for age-matched and gender-matched individuals from the general population in the Netherlands.*



< Back to page 144

Appendix Figure 3.2: *Estimated 5-year survival following the diagnosis of cardiovascular disease, non-AIDS-defining malignancy, diabetes mellitus, chronic kidney disease. Two reference groups are included: survival from date of entry into HIV care (after 1 January 2000), and from date of first AIDS diagnosis (after 1 January 2000). The numbers below the graph represent the number of subjects per stratum at risk at each time point.*

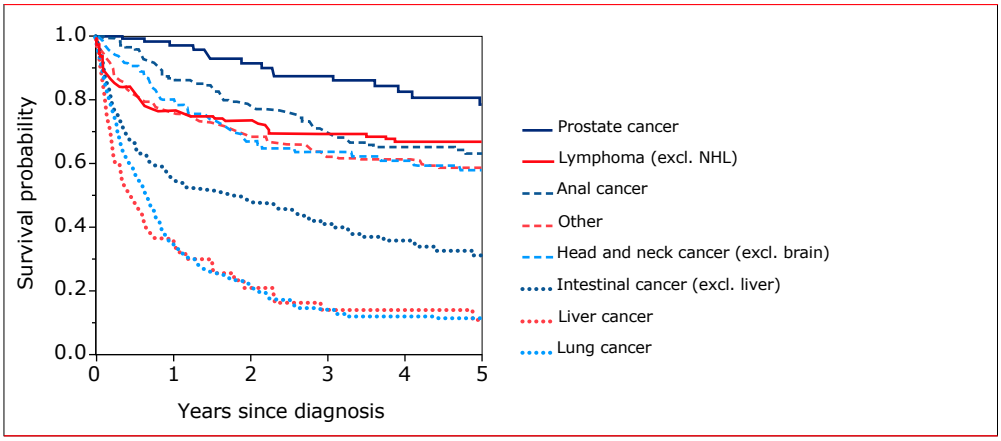


Time since diagnosis (years)	0	1	2	3	4	5
CVD	1,132	844	745	647	558	484
NADM	1,106	674	507	401	339	280
DM	1,186	1,004	888	791	675	577
CDK	1,657	1,287	1,011	801	631	482
In care for HIV	19,793	17,752	16,440	15,165	13,969	12,736
AIDS	3,681	3,097	2,847	2,581	2,394	2,192

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

< Back to page 171

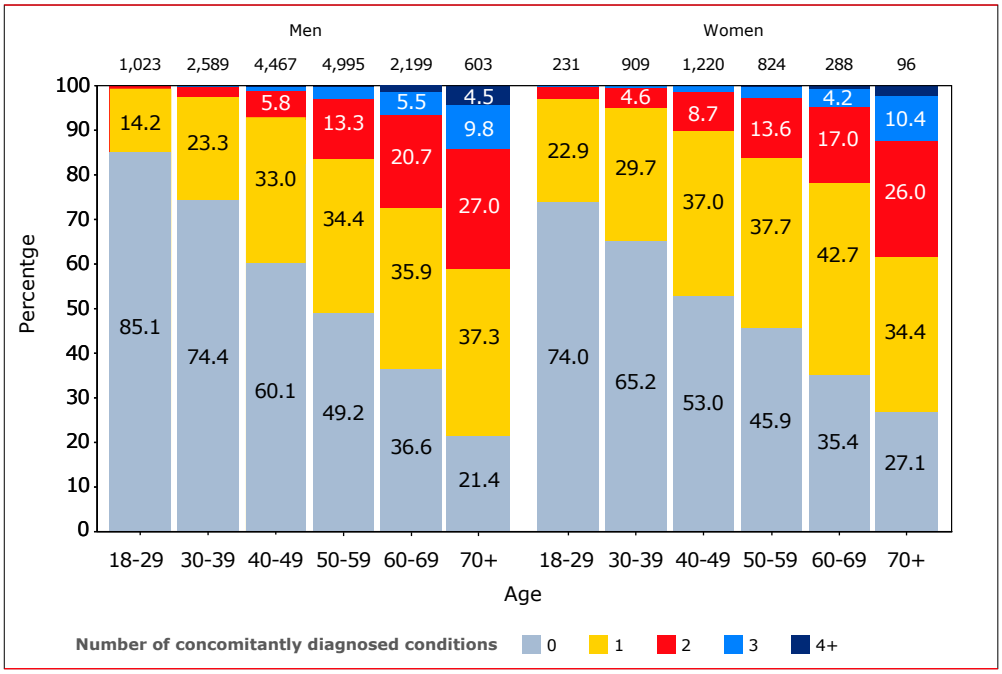
Appendix Figure 3.3: Estimated 5-year survival following the diagnosis of the most common non-AIDS-defining malignancies diagnosed between 1 January 2000 and 31 December 2017.



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

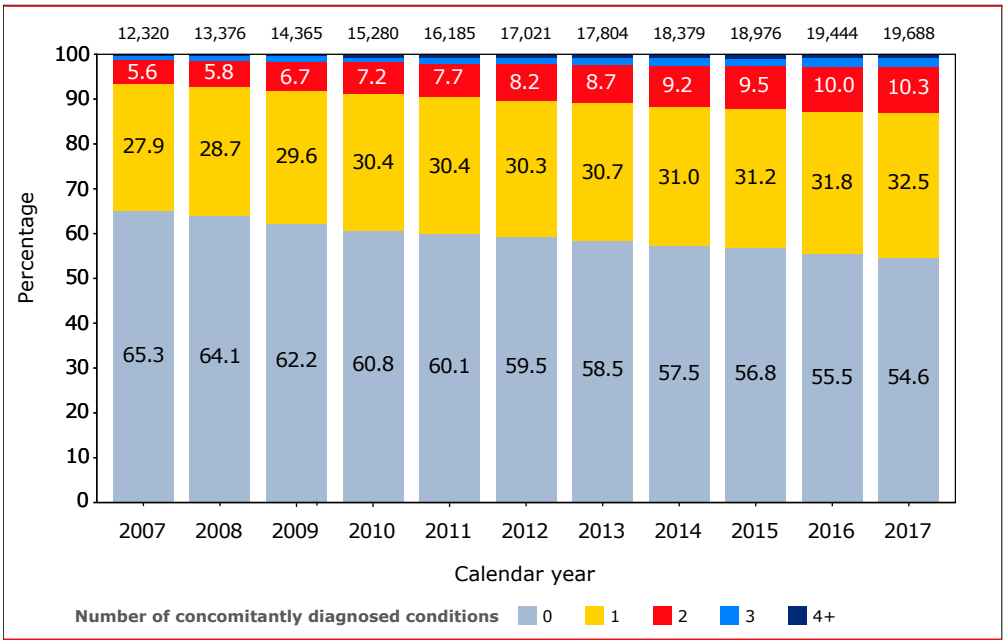
< Back to page 171

Appendix Figure 3.4: Prevalence of non-AIDS multimorbidity by gender in the adult population in 2017. 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.



< Back to page 173

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.



< Back to page 173

Appendix Table 3.1: Annual number of cases of death and first AIDS events among 25,524 HIV-1-positive individuals in the Netherlands recorded up to May 2017.

	AIDS			Death	
Calendar year	Number of AIDS events	AIDS ≥6 weeks after diagnosis	AIDS ≥4 weeks after start of cART	Number of deaths	Number of deaths ≥6 weeks after start of cART
1996	373	233	25	51	24
1997	312	154	52	87	63
1998	250	105	43	84	69
1999	235	116	56	92	90
2000	258	101	58	85	81
2001	259	127	63	83	79
2002	308	122	66	118	80
2003	315	140	73	142	117
2004	302	142	69	145	122
2005	378	177	89	142	116
2006	295	151	76	123	98
2007	332	170	91	152	126
2008	306	157	91	154	133
2009	302	138	76	161	142
2010	311	132	83	130	117
2011	256	121	75	151	135
2012	290	135	85	156	145
2013	257	124	90	149	140
2014	208	92	61	165	151
2015	233	113	90	161	153
2016	205	95	81	190	181
2017	114	32	26	126	119

Legend: cART=combination antiretroviral therapy.

< Back to page 144

Appendix Table 3.2: *Absolute number of causes of death among HIV-1-positive individuals during the periods 1996-2000, 2001-2005, 2006-2010, and 2011-2017.*

Causes of death	1996-2000	2001-2005	2006-2010	2011	2012	2013	2014	2015	2016	2017
AIDS										
AIDS - infection	68	119	149	35	15	23	17	7	1	.
AIDS - malignancy	58	63	61	3	13	10	5	13	4	.
AIDS - unclassifiable	97	65	20	3	4	.	4	9	16	10
Total	*223*	*247*	*230*	*41*	*32*	*33*	*26*	*29*	*21*	*10*
Non-AIDS malignancies	*30*	*96*	*134*	*32*	*43*	*38*	*41*	*39*	*48*	*39*
Cardiovascular disease										
Myocardial infarction	14	32	54	13	7	5	10	11	9	3
Stroke	4	11	14	3	4	3	4	3	7	2
Other CVD	6	20	16	8	4	3	12	10	16	3
Total	*24*	*63*	*84*	*24*	*15*	*11*	*26*	*24*	*32*	*8*
Non-AIDS infection	*24*	*42*	*31*	*4*	*7*	*6*	*10*	*6*	*12*	*7*
Liver disease	*17*	*30*	*62*	*8*	*9*	*10*	*11*	*6*	*5*	*4*
Lung disease	*4*	*11*	*33*	*7*	*4*	*9*	*5*	*14*	*13*	*8*
Non-natural death										
Accident or violence	6	11	21	1	5	3	5	2	7	1
Suicide	13	26	11	7	7	3	5	8	5	7
Euthanasia	3	3	2	2	.	1	1	.	.	4
Total	*22*	*40*	*34*	*10*	*12*	*7*	*11*	*10*	*12*	*12*
Alcohol and substance abuse	*10*	*13*	*19*	*1*	*4*	*4*	*4*	*2*	*5*	*1*
Other causes	*16*	*26*	*37*	*7*	*12*	*12*	*13*	*10*	*18*	*5*
Unknown	*29*	*62*	*56*	*17*	*18*	*19*	*18*	*21*	*24*	*32*
Total	**399**	**630**	**720**	**151**	**156**	**149**	**165**	**161**	**190**	**126**

< Back to page 145

Appendix Table 3.3: Adjusted risk factors for death and AIDS among HIV-1-positive individuals.

	Death			AIDS		
	RR (95% CI)	p-value	Overall p-value	RR (95% CI)	p-value	Overall p-value
Risk factors						
Male gender	1.34 (1.16-1.55)	<.001		1.01 (0.86-1.19)	0.877	
Region of birth						
Netherlands	1 (reference)		<.001	1 (reference)		0.118
Other	0.80 (0.73-0.89)	<.001		1.10 (0.98-1.24)	0.117	
HIV-1 transmission route						
Blood contact	0.74 (0.52-1.03)	0.078		0.90 (0.60-1.34)	0.611	
Heterosexual	1.10 (0.97-1.24)	0.132		0.89 (0.76-1.04)	0.149	
IDU	1.63 (1.35-1.97)	<.001		0.64 (0.49-0.84)	0.001	
MSM	1 (reference)		<.001	1 (reference)		0.002
Age*						
18-29	0.81 (0.59-1.11)	0.188	<.001	1.01 (0.81-1.24)	0.961	0.002
30-39	1 (reference)			1 (reference)		
40-49	1.38 (1.20-1.60)	<.001		1.07 (0.94-1.22)	0.308	
50-59	2.42 (2.10-2.80)	<.001		1.25 (1.08-1.46)	0.003	
60-69	4.16 (3.54-4.88)	<.001		1.37 (1.12-1.68)	0.003	
70+	7.26 (5.94-8.87)	<.001		1.84 (1.17-2.89)	0.008	
CD4 cell count**						
0-50	16.92 (14.22-20.15)	<.001	<.001	6.19 (4.96-7.72)	<.001	<.001
50-199	5.20 (4.52-5.99)	<.001		2.69 (2.26-3.19)	<.001	
200-349	2.21 (1.92-2.54)	<.001		1.51 (1.27-1.79)	<.001	
350-499	1.41 (1.22-1.63)	<.001		1.17 (0.98-1.39)	0.084	
500-749	1 (reference)			1 (reference)		
750+	0.73 (0.61-0.86)	<.001		1.02 (0.82-1.27)	0.856	
Per year longer on cART with HIV RNA >1,000 copies/ml	1.05 (1.03-1.07)	<.001	<.001	1.03 (1.00-1.06)	0.037	0.040
Treatment status						
Treatment-experienced at start cART	1.12 (1.02-1.24)	0.023		0.59 (0.52-0.68)	<.001	
Treatment-naive at start	1 (reference)			1 (reference)		
Prior AIDS event	1.88 (1.72-2.06)	<.001				
Hepatitis B virus positive	1.35 (1.17-1.55)	<.001		1.00 (0.82-1.21)	0.994	
Hepatitis C virus positive	1.45 (1.24-1.68)	<.001		1.30 (1.06-1.59)	0.010	

< Back to page 147

	Death			AIDS		
	RR (95% CI)	p-value	Overall p-value	RR (95% CI)	p-value	Overall p-value
Body mass index*						
<18	2.85 (2.51-3.24)	<.001	<.001			
18-25	1 (reference)					
25-30	0.69 (0.61-0.77)	<.001				
30+	0.84 (0.70-1.02)	0.075				
Smoking status						
Current smoker	1.46 (1.28-1.67)	<.001	<.001	0.76 (0.66-0.87)	<.001	<.001
Never smoker	1 (reference)			1 (reference)		
Past smoker	1.76 (1.53-2.04)	<.001		1.02 (0.86-1.22)	0.806	
Early cART***	0.67 (0.45-1.01)	0.055		0.95 (0.70-1.29)	0.752	

Time-updated.

Time-updated and lagged by 3 months.

cART started within 12 months after last HIV-negative test.

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

Appendix Table 3.4: *Lost to follow up (no follow up after 31 December 2017) 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)
<50	61	2,654	23.0 (17.6-29.5)	1	129	7.7 (0.2-43.2)	16	226	70.7 (40.4-114.8)
50-199	202	9,077	22.3 (19.3-25.5)	7	459	15.3 (6.1-31.4)	41	1,033	39.7 (28.5-53.9)
200-349	404	18,246	22.1 (20.0-24.4)	17	787	21.6 (12.6-34.6)	72	1,455	49.5 (38.7-62.3)
350-499	509	36,725	13.9 (12.7-15.1)	26	1,606	16.2 (10.6-23.7)	100	3,310	30.2 (24.6-36.7)
500-749	680	78,438	8.7 (8.0-9.3)	46	3,350	13.7 (10.1-18.3)	169	6,562	25.8 (22.0-29.9)
750+	414	85,465	4.8 (4.4-5.3)	27	3,579	7.5 (5.0-11.0)	132	7,391	17.9 (14.9-21.2)

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

< Back to page 148

	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)
	6	1,785	3.4 (1.2-7.3)	30	408	73.5 (49.6-104.9)	8	105	76.1 (32.8-149.9)
	31	5,626	5.5 (3.7-7.8)	116	1,687	68.8 (56.8-82.5)	7	273	25.7 (10.3-52.9)
	79	11,499	6.9 (5.4-8.6)	209	3,775	55.4 (48.1-63.4)	27	730	37.0 (24.4-53.8)
	109	23,568	4.6 (3.8-5.6)	253	6,863	36.9 (32.5-41.7)	21	1,377	15.3 (9.4-23.3)
	194	53,474	3.6 (3.1-4.2)	253	11,926	21.2 (18.7-24.0)	18	3,126	5.8 (3.4-9.1)
	130	61,918	2.1 (1.8-2.5)	115	9,874	11.6 (9.6-14.0)	10	2,703	3.7 (1.8-6.8)

Appendix Table 3.5: *Absolute number of first AIDS events among HIV-1-positive individuals during the periods 1996-2000, 2001-2005, 2006-2010, and 2011-2017.*

CDC event	1996-2000	2001-2005	2006-2010	2011-2017	Total	
	n	n	n	n	n	%
AIDS dementia complex / HIV encephalopathy	39	47	53	52	191	3.13
Cervical cancer	3	4	7	4	18	0.30
Bacterial pneumonia, recurrent	48	64	66	106	284	4.66
CMV ≥13 years	27	35	29	37	128	2.10
CMV pneumonitis	.	.	.	1	1	0.02
CMV retinitis	30	20	12	15	77	1.26
Candidiasis trachea, bronchi, lungs	7	13	7	7	34	0.56
Candidiasis oesophageal	256	234	249	279	1,018	16.71
Coccidioidomycosis, disseminated or extrapulmonary	.	.	1	.	1	0.02
Cryptococcosis, disseminated or extrapulmonary	21	32	32	14	99	1.62
Cryptosporidiosis	21	12	10	12	55	0.90
Cystoisosporiasis	3	9	5	.	17	0.28
Wasting syndrome due to HIV	49	57	77	103	286	4.69
Herpes simplex virus, chronic ulcer	.	1	.	1	2	0.03
Herpes simplex virus	32	41	60	46	179	2.94
Histoplasmosis, disseminated or extrapulmonary	9	12	10	8	39	0.64
Kaposi's sarcoma	154	150	186	162	652	10.70
Leishmaniasis, visceral	.	1	2	4	7	0.11
Lymphoma, primary, central nervous system	6	3	7	5	21	0.34
Microsporidiosis	11	1	3	1	16	0.26
Mycobacterium, other species/unidentified (disseminated/extrapulmonary)	21	12	7	11	51	0.84
Mycobacterium, other species/unidentified (pulmonary)	.	3	4	12	19	0.31
Mycobacterium avium/kansasii (disseminated/extrapulmonary)	25	21	28	12	86	1.41
Non-Hodgkin's lymphoma (NHL), HIV-related	59	87	80	115	341	5.60
Penicilliosis	.	.	1	.	1	0.02
Pneumocystis jirovecii extrapulmonary	1	1	3	.	5	0.08
Pneumocystis jirovecii pulmonary	334	296	323	337	1,290	21.17
Progressive multifocal leucoencephalopathy	18	25	35	25	103	1.69
Salmonella septicaemia, recurrent	2	.	.	.	2	0.03
Toxoplasmosis of the brain	70	98	56	54	278	4.56
Tuberculosis, extrapulmonary/disseminated	79	110	82	55	326	5.35
Tuberculosis, pulmonary	102	171	111	82	466	7.65
Total	**1,427**	**1,560**	**1,546**	**1,560**	**6,093**	**100.00**

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

< Back to page 148

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

	Men			Women		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	6	11,068	0.5 (0.2-1.2)	26	6,280	4.1 (2.7-6.1)
30-39	83	38,870	2.1 (1.7-2.6)	73	15,023	4.9 (3.8-6.1)
40-49	275	63,864	4.3 (3.8-4.8)	93	13,854	6.7 (5.4-8.2)
50-59	305	44,517	6.9 (6.1-7.7)	52	6,138	8.5 (6.3-11.1)
60-69	188	16,355	11.5 (9.9-13.3)	21	2,049	10.2 (6.3-15.7)
70+	40	3,488	11.5 (8.2-15.6)	5	576	8.7 (2.8-20.2)

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

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

	Men			Women		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	6	11,064	0.5 (0.2-1.2)	5	6,344	0.8 (0.3-1.8)
30-39	55	38,975	1.4 (1.1-1.8)	22	15,263	1.4 (0.9-2.2)
40-49	276	64,163	4.3 (3.8-4.8)	51	14,210	3.6 (2.7-4.7)
50-59	407	44,370	9.2 (8.3-10.1)	24	6,406	3.7 (2.4-5.6)
60-69	266	16,012	16.6 (14.7-18.7)	21	2,069	10.2 (6.3-15.5)
70+	79	3,272	24.1 (19.1-30.1)	7	567	12.3 (5.0-25.4)

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

< Back to page 150

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

	Men			Women		
Age	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**
18-29	33	7,901	4.2 (2.9-5.9)	10	3,302	3.0 (1.5-5.6)
30-39	90	23,283	3.9 (3.1-4.8)	25	9,099	2.7 (1.8-4.1)
40-49	148	43,392	3.4 (2.9-4.0)	71	10,278	6.9 (5.4-8.7)
50-59	264	35,022	7.5 (6.7-8.5)	109	5,010	21.8 (17.9-26.2)
60-69	345	13,501	25.6 (22.9-28.4)	75	1,433	52.3 (41.2-65.6)
70+	205	2,391	85.7 (74.4-98.3)	40	278	144.1 (102.9-196.2)

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

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

	Men			Women		
Age	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**
18-29	11	11,058	1.0 (0.5-1.8)	4	6,355	0.6 (0.2-1.6)
30-39	63	38,921	1.6 (1.2-2.1)	20	15,294	1.3 (0.8-2.0)
40-49	232	64,483	3.6 (3.1-4.1)	50	14,295	3.5 (2.6-4.6)
50-59	324	45,421	7.1 (6.4-8.0)	42	6,406	6.6 (4.7-8.9)
60-69	246	16,906	14.6 (12.8-16.5)	15	2,106	7.1 (4.0-11.7)
70+	86	3,434	25.0 (20.0-30.9)	8	599	13.4 (5.8-26.3)

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

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

	Men			Women		
Age	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**	**n**	**PYFU**	**Incidence/1000 PYFU (95% CI)**
18-29	1	11,080	0.1 (0.0-0.5)	2	6,362	0.3 (0.0-1.1)
30-39	25	39,052	0.6 (0.4-0.9)	6	15,323	0.4 (0.1-0.9)
40-49	175	64,509	2.7 (2.3-3.1)	26	14,349	1.8 (1.2-2.7)
50-59	225	45,234	5.0 (4.3-5.7)	15	6,495	2.3 (1.3-3.8)
60-69	154	16,784	9.2 (7.8-10.7)	9	2,127	4.2 (1.9-8.0)
70+	33	3,614	9.1 (6.3-12.8)	1	613	1.6 (0.0-9.1)

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

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

	Men			Women		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	5	11,064	0.5 (0.1-1.1)	2	6,350	0.3 (0.0-1.1)
30-39	29	39,039	0.7 (0.5-1.1)	16	15,279	1.0 (0.6-1.7)
40-49	86	64,818	1.3 (1.1-1.6)	25	14,319	1.7 (1.1-2.6)
50-59	130	45,761	2.8 (2.4-3.4)	9	6,494	1.4 (0.6-2.6)
60-69	97	17,205	5.6 (4.6-6.9)	10	2,121	4.7 (2.3-8.7)
70+	40	3,665	10.9 (7.8-14.9)	6	606	9.9 (3.6-21.5)

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

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

	Men		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	0	11,080	0.0 (.-0.3)
30-39	10	39,099	0.3 (0.1-0.5)
40-49	53	64,919	0.8 (0.6-1.1)
50-59	69	46,014	1.5 (1.2-1.9)
60-69	21	17,557	1.2 (0.7-1.8)
70+	3	3,869	0.8 (0.2-2.3)

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

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

	Men			Women		
Age	n	PYFU	Incidence/1000 PYFU (95% CI)	n	PYFU	Incidence/1000 PYFU (95% CI)
18-29	22	11,031	2.0 (1.2-3.0)	33	6,249	5.3 (3.6-7.4)
30-39	194	38,552	5.0 (4.3-5.8)	109	14,911	7.3 (6.0-8.8)
40-49	738	62,362	11.8 (11.0-12.7)	182	13,496	13.5 (11.6-15.6)
50-59	931	41,820	22.3 (20.9-23.7)	106	5,853	18.1 (14.8-21.9)
60-69	563	14,268	39.5 (36.3-42.9)	49	1,905	25.7 (19.0-34.0)
70+	157	2,639	59.5 (50.6-69.6)	15	476	31.5 (17.7-52.0)

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

Appendix Table 3.7: Adjusted risk factors for non-AIDS-defining morbidity.

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value
Male gender	1.28 (1.15-1.43)	<.001	.	1.59 (1.29-1.97)	<.001	.
Region of birth						
Netherlands	1 (reference)	.	<.001	1 (reference)	.	0.009
Other	0.88 (0.82-0.95)	<.001	.	0.84 (0.73-0.96)	0.010	.
HIV-1 transmission route						
MSM	1 (reference)	.	<.001	1 (reference)	.	0.005
Heterosexual	0.94 (0.87-1.03)	0.175	.	1.24 (1.06-1.45)	0.009	.
IDU	1.03 (0.85-1.25)	0.735	.	1.33 (0.95-1.86)	0.094	.
Blood contact	0.75 (0.58-0.98)	0.035	.	1.39 (0.92-2.09)	0.113	.
Age*						
18-29	0.76 (0.58-0.99)	0.040	<.001	0.46 (0.24-0.89)	0.022	<.001
30-39	1 (reference)	.	.	1 (reference)	.	.
40-49	2.10 (1.85-2.38)	<.001	.	2.64 (2.06-3.38)	<.001	.
50-59	4.92 (4.34-5.57)	<.001	.	5.32 (4.15-6.83)	<.001	.
60-69	9.27 (8.12-10.58)	<.001	.	9.75 (7.49-12.70)	<.001	.
70+	18.88 (16.21-22.00)	<.001	.	14.30 (10.31-19.82)	<.001	.
CD4 cell count**						
<50	3.71 (2.99-4.60)	<.001	<.001	3.39 (2.22-5.17)	<.001	<.001
50-199	1.60 (1.40-1.83)	<.001	.	1.65 (1.27-2.14)	<.001	.
200-349	1.13 (1.02-1.24)	0.014	.	1.26 (1.04-1.53)	0.016	.
350-499	0.98 (0.91-1.07)	0.715	.	1.08 (0.91-1.27)	0.399	.
500-749	1 (reference)	.	.	1 (reference)	.	.
≥750	0.98 (0.91-1.06)	0.621	.	1.25 (1.06-1.46)	0.007	.
Per year longer with CD4 <200 cells/mm³	0.99 (0.98-1.01)	0.564	.	1.00 (0.97-1.04)	0.847	.
Prior AIDS event	1.21 (1.14-1.29)	<.001	.	1.15 (1.01-1.31)	0.031	.
Per year longer on cART while HIV RNA>1000 copies/ml	1.01 (0.99-1.03)	0.254	.	1.02 (0.98-1.06)	0.287	.
Treatment status						
Not (yet) started cART	1.13 (1.00-1.27)	0.049	<.001	1.07 (0.85-1.35)	0.580	0.021
Treatment-experienced at start cART	1.49 (1.38-1.61)	<.001	.	1.25 (1.07-1.47)	0.006	.
Treatment-naive at start	1 (reference)	.	.	1 (reference)	.	.
Per year longer on cART	1.02 (1.01-1.02)	<.001	.	1.00 (0.98-1.01)	0.922	.
Early cART within 12 months after last HIV-negative	0.87 (0.71-1.07)	0.177	.	1.09 (0.74-1.60)	0.661	.

< Back to page 152

	Non-AIDS-defining malignancy			Diabetes mellitus			Chronic kidney disease		
	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value
	1.15 (0.93–1.42)	0.201	.	1.25 (1.05–1.48)	0.014	.	0.50 (0.43–0.60)	<.001	.
	1 (reference)	.	0.008	1 (reference)	.	<.001	1 (reference)	.	<.001
	0.82 (0.71–0.95)	0.008	.	1.41 (1.24–1.61)	<.001	.	1.55 (1.38–1.75)	<.001	.
	1 (reference)	.	0.008	1 (reference)	.	<.001	1 (reference)	.	0.054
	1.05 (0.88–1.25)	0.580	.	1.53 (1.30–1.79)	<.001	.	1.03 (0.88–1.20)	0.754	.
	1.55 (1.11–2.15)	0.009	.	1.49 (1.04–2.14)	0.030	.	1.67 (1.23–2.25)	<.001	.
	1.71 (1.15–2.54)	0.008	.	1.48 (0.98–2.23)	0.064	.	1.06 (0.70–1.59)	0.786	.
	0.74 (0.44–1.25)	0.258	<.001	0.60 (0.40–0.88)	0.009	<.001	0.93 (0.63–1.37)	0.718	<.001
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	2.37 (1.84–3.06)	<.001	.	1.51 (1.25–1.83)	<.001	.	1.47 (1.16–1.87)	0.001	.
	4.67 (3.62–6.02)	<.001	.	2.34 (1.91–2.86)	<.001	.	3.69 (2.94–4.63)	<.001	.
	9.12 (6.96–11.95)	<.001	.	4.16 (3.32–5.21)	<.001	.	13.17 (10.46–16.57)	<.001	.
	15.88 (11.47–21.99)	<.001	.	4.43 (3.11–6.32)	<.001	.	41.95 (32.52–54.13)	<.001	.
	3.18 (1.98–5.13)	<.001	<.001	8.46 (6.19–11.56)	<.001	<.001	2.15 (1.33–3.48)	0.002	<.001
	2.15 (1.65–2.81)	<.001	.	2.21 (1.71–2.85)	<.001	.	1.62 (1.27–2.08)	<.001	.
	1.50 (1.24–1.81)	<.001	.	1.12 (0.91–1.37)	0.286	.	1.22 (1.02–1.45)	0.031	.
	1.10 (0.93–1.31)	0.256	.	0.99 (0.83–1.18)	0.882	.	1.04 (0.90–1.22)	0.577	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	0.87 (0.73–1.04)	0.119	.	1.14 (0.96–1.34)	0.129	.	0.98 (0.85–1.13)	0.776	.
	0.96 (0.92–0.99)	0.026	.	0.96 (0.92–1.00)	0.054	.	1.00 (0.97–1.04)	0.836	.
	1.27 (1.11–1.46)	<.001	.	1.30 (1.14–1.48)	<.001	.	1.10 (0.98–1.24)	0.113	.
	0.99 (0.95–1.03)	0.666	.	1.02 (0.98–1.05)	0.343	.	0.98 (0.95–1.01)	0.240	.
	1.44 (1.16–1.80)	0.001	<.001	1.80 (1.47–2.21)	<.001	<.001	0.70 (0.53–0.92)	0.012	0.002
	1.22 (1.03–1.45)	0.023	.	1.39 (1.18–1.65)	<.001	.	1.23 (1.05–1.45)	0.012	.
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	1.01 (0.99–1.02)	0.425	.	1.02 (1.00–1.04)	0.017	.	0.99 (0.98–1.00)	0.138	.
	0.58 (0.34–1.00)	0.048	.	0.88 (0.55–1.41)	0.596	.	0.99 (0.72–1.36)	0.945	.

	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*						
<18	1.39 (1.18-1.64)	<.001	<.001	1.15 (0.82-1.62)	0.408	0.003
18-25	1 (reference)	.	.	1 (reference)	.	.
25-30	1.11 (1.04-1.18)	0.003	.	0.99 (0.86-1.13)	0.839	.
30+	1.42 (1.28-1.57)	<.001	.	1.09 (0.87-1.36)	0.466	.
Hepatitis B virus positive	0.92 (0.82-1.04)	0.199	.	0.99 (0.79-1.25)	0.930	.
Hepatitis C virus positive	0.91 (0.81-1.03)	0.122	.	0.96 (0.76-1.20)	0.706	.
Hypertension	1.25 (1.17-1.33)	<.001	.	1.27 (1.12-1.44)	<.001	.
Smoking status						
Current smoker	1.22 (1.13-1.31)	<.001	<.001	1.87 (1.60-2.20)	<.001	<.001
Never smoker	1 (reference)	.	.	1 (reference)	.	.
Past smoker	1.43 (1.32-1.56)	<.001	.	1.54 (1.28-1.85)	<.001	.
Calendar year period						
2000-2005	0.96 (0.87-1.06)	0.402	0.309	1.53 (1.28-1.83)	<.001	<.001
2006-2010	1.03 (0.96-1.11)	0.398	.	1.29 (1.12-1.49)	<.001	.
2011-2017	1 (reference)	.	.	1 (reference)	.	.
Recent use of ABC***		.	.	1.54 (1.35-1.76)	<.001	.
Per year longer on LPV/r		.	.	1.01 (0.99-1.03)	0.236	.
Per year longer on IDV		.	.	1.00 (0.99-1.01)	0.658	.
Per year longer on ZDV		.	.		.	.
Per year longer on d4T		.	.		.	.
Per year longer on ddI		.	.		.	.
Per year longer on TDF		.	.		.	.
Prior cardiovascular event		.	.		.	.
Prior diabetes		.	.		.	.
Current use of cobicistat		.	.		.	.
Current use of dolutegravir		.	.		.	.

**Time-updated.*

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

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

Legend: *CKD=chronic kidney disease; IDU=injecting drug use; cART=combination antiretroviral therapy; LOP/r=lopinavir/ritonavir; IDV=indinavir; ABC=abacavir; ZDV=zidovudine; d4T=stavudine; ddI=didanosine; 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			Chronic kidney disease		
	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value	IRR (95% CI)	p-value	Overall p-value
	1.88 (1.43-2.49)	<.001	<.001	1.40 (0.95-2.06)	0.086	<.001	4.66 (3.84-5.66)	<.001	<.001
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	0.80 (0.69-0.93)	0.003	.	2.04 (1.76-2.35)	<.001	.	0.42 (0.36-0.49)	<.001	.
	0.80 (0.61-1.03)	0.084	.	4.08 (3.44-4.85)	<.001	.	0.21 (0.15-0.29)	<.001	.
	1.60 (1.31-1.96)	<.001	.	1.11 (0.89-1.40)	0.357	.	1.31 (1.06-1.61)	0.012	.
	1.03 (0.82-1.30)	0.777	.	1.15 (0.91-1.45)	0.245	.	1.21 (1.00-1.47)	0.054	.
	1.03 (0.90-1.18)	0.674	.	1.19 (1.04-1.36)	0.011	.	0.94 (0.83-1.06)	0.305	.
	1.56 (1.32-1.84)	<.001	<.001	0.86 (0.74-1.01)	0.062	0.083	1.20 (1.04-1.38)	0.013	0.006
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
	1.38 (1.14-1.67)	0.001	.	1.07 (0.90-1.27)	0.469	.	1.18 (1.01-1.38)	0.037	.
	0.89 (0.73-1.09)	0.251	0.031	1.27 (1.05-1.53)	0.013	0.016		.	.
	1.13 (0.98-1.32)	0.097	.	1.20 (1.04-1.40)	0.015	.	0.96 (0.83-1.11)	0.557	0.555
	1 (reference)	.	.	1 (reference)	.	.	1 (reference)	.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.	1.01 (1.00-1.01)	0.020	.		.	.
		.	.	1.01 (0.99-1.02)	0.338	.		.	.
		.	.	1.00 (0.99-1.01)	0.374	.		.	.
		.	.		.	.	1.00 (0.99-1.01)	0.995	.
		.	.		.	.	1.68 (1.40-2.02)	<.001	.
		.	.		.	.	1.35 (1.10-1.66)	0.004	.
		.	.		.	.	1.71 (1.40-2.09)	<.001	.
		.	.		.	.	2.76 (2.39-3.20)	<.001	.

Appendix Table 3.8: *Specific CDC-B and CDC-C (AIDS) events occurring in individuals on cART with undetectable viral load between 2000 and 2017.*

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
CDC-B events	Bacillary angiomatosis	1	0.0%	0	0.0%
	Candidiasis, oropharyngeal	657	22.3%	57	26.9%
	Candidiasis, vulvovaginal	54	1.8%	1	0.5%
	Cervical dysplasia or carcinoma in situ	532	18.1%	9	4.2%
	Diarrhoea of unknown origin >1 month	66	2.2%	1	0.5%
	Fever of unknown origin >1 month	6	0.2%	0	0.0%
	Herpes simplex virus, mucocutaneous	19	0.6%	1	0.5%
	Herpes zoster, multidermatomal or 2+ episodes	219	7.4%	9	4.2%
	Myelopathy, HIV-related	11	0.4%	0	0.0%
	Neuropathy, peripheral, HIV-related	74	2.5%	1	0.5%
	Nocardiosis	1	0.0%	1	0.5%
	Oral hairy leukoplakia	50	1.7%	1	0.5%
	Pelvic inflammatory disease	4	0.1%	0	0.0%
	Thrombocytopenia, HIV-related	100	3.4%	5	2.4%
	Weight loss (> 10%) of unknown origin	36	1.2%	2	0.9%
Subtotal		**1,830**	**62.1%**	**88**	**41.5%**
CDC-C events	AIDS dementia complex / HIV encephalopathy	46	1.6%	5	2.4%
	Candidiasis, esophageal	201	6.8%	21	9.9%
	Candidiasis trachea, bronchi, lungs	9	0.3%	2	0.9%
	Cervical cancer, invasive	7	0.2%	1	0.5%
	Cytomegalovirus disease (not lymph node, liver or spleen)	19	0.6%	5	2.4%
	Cytomegalovirus retinitis	14	0.5%	2	0.9%
	Coccidioidomycosis, disseminated/ extrapulmonary	1	0.0%	0	0.0%
	Cryptococcosis extrapulmonary	16	0.5%	6	2.8%
	Cryptosporidiosis, chronic intestinal	9	0.3%	3	1.4%
	Herpes simplex virus: chronic bronchitis, pneumonitis, esophagitis	62	2.1%	6	2.8%
	Histoplasmosis, disseminated or extrapulmonary	4	0.1%	3	1.4%
	Isosporiasis, chronic intestinal (>1 month)	1	0.0%	0	0.0%
	Kaposi sarcoma	87	3.0%	5	2.4%
	Leishmaniasis, visceral	5	0.2%	1	0.5%
	Lymphoma, non-Hodgkin's lymphoma	113	3.8%	7	3.3%

< Back to page 149

CD4 category										
50–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
166	29.9%	135	20.5%	101	17.4%	125	20.7%	73	21.6%
5	0.9%	10	1.5%	17	2.9%	15	2.5%	6	1.8%
54	9.7%	122	18.6%	123	21.2%	138	22.8%	86	25.4%
6	1.1%	16	2.4%	11	1.9%	23	3.8%	9	2.7%
1	0.2%	2	0.3%	0	0.0%	1	0.2%	2	0.6%
4	0.7%	1	0.2%	5	0.9%	4	0.7%	4	1.2%
26	4.7%	52	7.9%	46	7.9%	54	8.9%	32	9.5%
4	0.7%	2	0.3%	1	0.2%	1	0.2%	3	0.9%
8	1.4%	17	2.6%	24	4.1%	13	2.2%	11	3.3%
0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
13	2.3%	10	1.5%	9	1.6%	10	1.7%	7	2.1%
0	0.0%	1	0.2%	1	0.2%	1	0.2%	1	0.3%
19	3.4%	24	3.7%	18	3.1%	24	4.0%	10	3.0%
5	0.9%	8	1.2%	7	1.2%	8	1.3%	6	1.8%
312	**56.1%**	**400**	**60.9%**	**363**	**62.6%**	**417**	**69.0%**	**250**	**74.0%**
8	1.4%	10	1.5%	9	1.6%	7	1.2%	7	2.1%
50	9.0%	49	7.5%	33	5.7%	29	4.8%	19	5.6%
2	0.4%	3	0.5%	0	0.0%	1	0.2%	1	0.3%
1	0.2%	2	0.3%	1	0.2%	2	0.3%	0	0.0%
2	0.4%	3	0.5%	5	0.9%	1	0.2%	3	0.9%
5	0.9%	2	0.3%	4	0.7%	1	0.2%	0	0.0%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
6	1.1%	3	0.5%	0	0.0%	1	0.2%	0	0.0%
0	0.0%	1	0.2%	3	0.5%	1	0.2%	1	0.3%
6	1.1%	13	2.0%	17	2.9%	16	2.6%	4	1.2%
0	0.0%	0	0.0%	0	0.0%	1	0.2%	0	0.0%
0	0.0%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
9	1.6%	23	3.5%	20	3.4%	21	3.5%	9	2.7%
3	0.5%	1	0.2%	0	0.0%	0	0.0%	0	0.0%
30	5.4%	25	3.8%	25	4.3%	21	3.5%	5	1.5%

		All events		0–50	
	CDC event	**n**	**%**	**n**	**%**
	Lymphoma, primary, of brain	5	0.2%	0	0.0%
	Microsporidiosis	3	0.1%	1	0.5%
	MAI / M. kansasii, disseminated/extrapulmonary	21	0.7%	4	1.9%
	Mycobacterium, other/unidentified (disseminated/extrapulmonary)	6	0.2%	1	0.5%
	Pneumocystis jirovecii pneumonia	58	2.0%	15	7.1%
	Pneumonia, recurrent (in a 1-year period)	278	9.4%	15	7.1%
	Progressive multifocal leucoencephalopathy	17	0.6%	4	1.9%
	Toxoplasmosis of the brain	16	0.5%	5	2.4%
	Tuberculosis, extrapulmonary	36	1.2%	3	1.4%
	Tuberculosis, pulmonary	62	2.1%	4	1.9%
	Wasting syndrome due to HIV	15	0.5%	5	2.4%
	Other CDC C-event, specify	6	0.2%	0	0.0%
Subtotal		**1,117**	**37.9%**	**124**	**58.5%**
Total		**2,947**	**100.0%**	**212**	**100.0%**

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

CD4 category										
50–199		200–349		350–499		500–749		750+	
n	%	n	%	n	%	n	%	n	%
1	0.2%	2	0.3%	1	0.2%	1	0.2%	0	0.0%
1	0.2%	0	0.0%	0	0.0%	0	0.0%	1	0.3%
8	1.4%	4	0.6%	2	0.3%	1	0.2%	2	0.6%
1	0.2%	3	0.5%	0	0.0%	1	0.2%	0	0.0%
20	3.6%	9	1.4%	8	1.4%	4	0.7%	2	0.6%
50	9.0%	70	10.7%	65	11.2%	55	9.1%	23	6.8%
6	1.1%	3	0.5%	2	0.3%	2	0.3%	0	0.0%
6	1.1%	3	0.5%	1	0.2%	1	0.2%	0	0.0%
7	1.3%	6	0.9%	5	0.9%	10	1.7%	5	1.5%
14	2.5%	19	2.9%	12	2.1%	8	1.3%	5	1.5%
6	1.1%	1	0.2%	2	0.3%	1	0.2%	0	0.0%
2	0.4%	1	0.2%	2	0.3%	0	0.0%	1	0.3%
244	**43.9%**	**257**	**39.1%**	**217**	**37.4%**	**187**	**31.0%**	**88**	**26.0%**
556	**100.0%**	**657**	**100.0%**	**580**	**100.0%**	**604**	**100.0%**	**338**	**100.0%**