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ARTICLE

Trends over time in underlying causes of death amongst HIV-positive individuals from 1999 to 2011

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Abstract

Background: Over time, an evolution in the causes of morbidity and mortality among HIV-positive individuals has been reported. It is increasingly important to monitor trends in causes of death to devise appropriate prevention and management strategies.
Methods: Individuals from the D:A:D Study were followed from January 1999 until death, loss-to-follow-up or February 2011, whichever occurred first. Relative rates were calculated using Poisson regression.
Results: There were 3,909 deaths in 49,731 individuals during 308,719 person-years (rate=12.7/1000 person-years; 95% CI 12.3-13.1). Leading underlying causes were: AIDS-related (28.7%), non-AIDS-defining cancers (15.1%), liver disease (13.2%) and cardiovascular disease (11.1%). Rates of all-cause death fell from 17.5/1000 person-years in 1999/2000 to 9.1 in 2009/2011; similar trends were seen in death rates for AIDS-related (5.9-2.0), liver disease (2.7-0.9) and cardiovascular disease (1.8-0.9). However, non-AIDS cancers death rates remained stable (1.6-2.1). Decreases in AIDS-related death rates were no longer evident after accounting for factors that changed over time, including CD4 cell count. However, all-cause, liver disease and cardiovascular disease death rates remained decreasing over time. The percentage of all deaths

that were AIDS-related (34.0% in 1999/2000-22.5% in 2009/2011) and liver-related (15.6%-10.2%) decreased over time, whereas non-AIDS cancers increased (9.4%-22.7%).
Conclusions: Recent reductions in rates of AIDS-related deaths are linked with continued improvement in CD4 cell count. We hypothesize that the markedly reduced rates of liver disease and cardiovascular disease deaths over time could be explained by improved use of non-HIV specific preventive interventions. Non-AIDS cancer is now the leading non-AIDS cause and without any evidence of improvement. No other emerging trends in causes of unexpected deaths were observed.

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Background

In settings with access to antiretroviral therapy (ART), there have been dramatic reductions in AIDS-related mortality amongst HIV-positive individuals in care, with life expectancy now approaching that seen in the general population[1-3]. As a result, the relative importance of other traditionally non-AIDS related morbidities have increased, and a wider range of complications has been observed than in previous years[1].
Rates of some non-AIDS related morbidities may be expected to be higher than those seen in the general population for three main reasons. Firstly the HIV-positive population in resource-rich settings has a high level of traditional risk factors for non-AIDS morbidities, such as smoking and hepatitis co-infection[4-6]. Secondly, recent evidence suggests that the persistent immunodeficiency, immune dysregulation, immune activation and inflammation associated with HIV infection, including in patients on ART, may increase the risk of some of these morbidities[7,8]. Thirdly, antiretroviral-related adverse events, such as dyslipidamia and diabetes, may also play a role. Although one cannot dispute the clear benefits of ART, life-long exposure to these drugs is likely to be required. Thus, long-term surveillance for emerging, not-yet-identified serious adverse events caused by extended exposure to these novel agents is important. Reporting of such events using a passive clinician-initiated approach will likely be insensitive to detect emerging issues should they occur. A major aim of the D:A:D Study is to be able to identify whether there is any emerging serious toxicity linked with use of ART, as demonstrated by an increase in the rates of mortality either from a particular organ system, from cancers, or other, as yet unanticipated, causes.
The aim of this project is to investigate trends over time in all-cause mortality and for specific causes of death in the period from 1999-2011 within the D:A:D Study. We examined whether any observed changes over time in death rates (overall and cause-specific) can be explained by changes in the characteristics of the HIV-positive population, including HIV immunological and virological status. Finally, we assessed whether any unexpected increases in rates of death from any specific cause emerged.

Methods

Verification and classification of causes of death
Participants included were from the Data collection on Adverse events of anti-HIV Drugs (D:A:D) Study[9]. It is a collaboration of 11 cohort studies following 49,731 HIV-1-infected individuals receiving care at 212 clinics in Europe, USA, and Australia. Further information on the study is available at http://www.cphiv.dk/DAD/About/tabid/106/Default.aspx. All participants were under active follow-up in their cohorts at the time of D:A:D enrolment. Prospective follow-up began from January 1999 onwards, regardless of ART status. Participants were recruited during three recruitment waves: 1999-2001, 2004, and 2010. All clinical outcomes, including deaths, are reported in real time. For 84% of all reported deaths, the sites provided a completed-case report

form and so the cause of death could be centrally validated. Consistent classification categories for causes of death was used across the entire study period using adapted ICD-10 codes, with the Cause of Death (CoDe) form used from 2004 onwards (see www.cphiv.dk)[10].

Although data on both the underlying and other contributing causes of death are available, only the underlying cause is considered here and is referred to as 'cause of death' hereafter. They were grouped for analysis into the following five categories: AIDS-related; Cardiovascular disease related; Liver disease-related; Non-AIDS Cancers (i.e. excluding Kaposi's sarcoma, non-Hodgkin lymphoma and cervical cancer); and Other/unknown.

Statistical methods

Individuals were followed from D:A:D entry to the first of death, six months after last clinic visit or 1st February 2011. Although follow-up was available until 1st February 2012, the last year was excluded to account for underascertainment due to delayed reporting.

Crude and age-standardised (adjusted to the age distribution of the cohort in 2003/2004, using Dobson's approach to calculate corresponding confidence intervals[11]) death incidence rates were estimated for each two-year follow-up period. Unadjusted and adjusted relative rates (RRs) for the association of calendar time with all cause and cause-specific mortality were calculated using Poisson regression. Factors adjusted for were: (fixed-time variables) age at study entry (per 5 years), gender (male or female), ethnicity (white, black African or other), mode of HIV acquisition (men who have sex with men, heterosexual, intravenous drug user (IDU) or other/unknown) and (time-updated variables) hepatitis B virus (HBV) status (yes, no or unknown; defined as HBsAg positive, HBeAg positive or HBV DNA positive/anti-Hbe positive), hepatitis C virus (HCV) status (yes, no or unknown; defined as HCVAb positive), smoking status (current, former, ex-smoker or unknown), diabetes (yes or no; centrally validated endpoint; see www.cphiv.dk), hypertension (yes or no; defined as systolic blood pressure>140 mmHg; diastolic blood pressure>90 mmHg or receiving anti-hypertensives), HIV RNA viral load (VL; on ART with VL<400 copies/ml, on ART with VL≥400 copies/ml, off ART with VL<10,000 copies/ml or off ART with VL ≥10,000 copies/ml), body mass index (BMI; <18, 18 to ≤26, >26 to ≤30 or >30 kg/m^2) and CD4 cell count (per 50 cells/mm^3). All analyses were repeated, restricting to the person-years of follow-up amongst which study participants had viral load<400 copies/ml. This was to investigate trends over time in death rates amongst those with an optimal response to ART. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Sensitivity analyses

We remodelled all multivariable Poisson Regression models without adjusting for VL. Next, as individuals were censored at the time of death if they died from a cause other than the one under consideration, our primary analyses did not explicitly account for the presence of competing risks. This was investigated by excluding individuals who died from other causes from cause-specific analyses[12]. All analyses were remodelled according to the following demographic sub-groups: HBV status, HCV status, gender, HIV acquisition risk, smoking status, BMI and age group. Analyses were remodelled using multiple imputation to account for unknown causes of death, following the standard approach[13]. Finally, analyses were remodelled stratified by wave of recruitment into the D:A:D study.

Role of the funding source

The funders had no direct role in study design, data collection, analysis, interpretation, report writing, or the decision to submit for publication. The corresponding author had full access to all data and responsibility for submission for publication.

Results

Participant population

The 49,731 D:A:D Study participants are summarized in Table 1. Most are male (74%), the most common mode of HIV acquisition was sex between men (44%), and the median age at study entry was 38 years. The median CD4 cell count at study entry was 400 cells/mm^3 and 61% had ever received ART. Information on how the characteristics of the population have changed over time is also provided in Table 1. Compared to those who were under follow-up on 1st January 2001 (the time at which recruitment of the first wave of participants was nearing completion), those who were under follow-up in 2011 were less likely to have acquired HIV through intravenous drug use, less likely to be HBV or HCV positive, less likely to be a smoker, and more likely to have hypertension or diabetes. They were also more likely to be successfully treated on ART (with viral load<400 copies/ml), had a higher median CD4 count and a longer median length of time spent on ART.
A total of 3,909 deaths occurred. Compared to the general D:A:D population, there was a higher proportion of deaths in men, HCV positive individuals, those with an IDU risk for HIV acquisition, smokers and individuals with a previous AIDS diagnosis and the median CD4 cell count at study entry was lower (Table 1)

Causes of death
The most common cause of death observed over the whole study period was AIDS-related (28.7%), followed by non-AIDS cancers (15.1%), liver disease (13.2) and cardiovascular (11.1%; Table 2). The most common 'other' causes of death were invasive bacterial infection (6.6%) and suicide (3.8%). Although it has remained the most common cause over the whole follow-up period, the percentage of all deaths attributable to AIDS has fallen from 34.0% in 1999/2000 to 22.5% in 2009-2011 (Figure 1; p<0.0001, chi-squared test). The percentage of liver-related deaths also fell (15.6% to 10.2%). In contrast, the proportion of all deaths that were from non-AIDS cancers has increased (9.4% to 22.7%). It is now the leading non-AIDS cause, and is equally as common as AIDS-related deaths.

Rates of death over time
The 3,909 deaths occurred over 308,719 person-years of follow-up (median 5.8 person-years; inter-quartile range 3.3, 9.9). This corresponds to a crude incidence mortality rate of 12.7 per 1,000 person-years (95% confidence interval [CI] 12.3, 13.1). The rate of death has decreased from 17.5 per 1,000 person-years in 1999/2000 to 9.1 in 2009-2011. This decline in overall death rate remains after accounting for an aging population through use of age-standardised estimates (Figure 2a and Supplementary Table 3). Similarly, declines were seen for AIDS-related, liver disease and cardiovascular deaths. In contrast, the rate of non-AIDS cancer deaths remained relatively constant, at 1.6 per 1000 person-years in 1999/2000 and 2.1 per 1000 person-years in 2009-2011. This information was also reflected in the unadjusted rate ratios (Table 4).
After adjusting for the potential confounders listed in the methods, the rate of all-cause mortality still declined (Table 4), suggesting that changes in these factors could not explain the decline in death rates seen over time. For example, compared to 1999/2000, the rate of death in 2009-2011 was reduced by 28% (RR=0.72; 95% CI 0.61, 0.83). Similarly, liver disease and cardiovascular death rates were substantially reduced in later years even after accounting for changes in demographic factors over time. Compared to 1999/2000, rates of liver disease death in 2009-2011 were 52% lower and rates of cardiovascular deaths were 67% lower. In contrast, changes in factors over time did explain much of the observed decline in rate of death from AIDS-related causes, as the adjusted RRs in Table 4 all approached one. Much of this was explained by improvements over time in the CD4 cell count; when this factor was not adjusted for in a post-hoc analyses the RRs were similar to those seen in the unadjusted analyses. Finally, adjustments for factors that may have changed over time did not affect the pattern for non-AIDS cancers, with rates remaining constant across the follow-up period.

Sub-group of individuals with viral load<400 copies/ml
There were 1859 deaths in 194,338 person-years of follow-up during which the current viral load was <400 copies/ml. As expected, this corresponded to a much lower overall death rate (9.6 per

1000 person-years; 95% CI 9.1, 10.0), particularly from AIDS-related causes (rate=1.4; 95% CI 1.2, 1.6). Figure 2b and Supplementary Table 5 display the age-adjusted and crude death rates from each specific cause over time. There was lower statistical power to explore trends over time, but there was no evidence of different trends compared to the main analysis. Furthermore, the adjusted rate ratios for changes in over time (Supplementary Table 6) found no evidence of an increasing trend from any cause, although confidence intervals are wider reflecting greater estimate uncertainty.
Results were consistent in all sensitivity analyses performed, including the results of multiple imputation.

Discussion

Death rates amongst HIV-positive individuals with access to care and antiretroviral therapy across the study period have continued to decline. Currently, there is no indication of any increase in risk of death from any specific cause as a potential result of long term adverse effects of ART, and deaths from causes other than AIDS, cardiovascular disease, liver and non-AIDS cancers remain low. This provides continued evidence of the substantial net benefits of ART.
It is notable that there have been apparent continued declines in mortality due to most causes, even after accounting for any effects of uncontrolled HIV replication, immunological improvements as measured by the CD4 count and age. This was reflected in the adjusted rate ratios displayed in Table 5, and the sub-group analysis considering those with current viral load<400 copies/ml. It is concerning however that the overall rate in non-AIDS Cancers has remained constant over time, and suggests that this is an important area that needs further research.
A number of studies of HIV-positive populations have demonstrated dramatic decreases in AIDS-related deaths over time[1,14,15]. It is encouraging that these improvements have continued into the most recent time period. The observed decline could be largely explained by changes in the CD4 cell count, most likely as a result of successful ART rather than changes in included participants over time, as results were consistent when stratifying by recruitment wave. Any residual improvements not explained by the CD4 cell count may be due to better management of AIDS-related conditions and increased use of prophylactic treatments. However, despite all of the improvements in AIDS-related morbidity, it remains the leading cause of death in this population[16]. Continued efforts to ensure good ART adherence and to diagnose more individuals at an earlier stage before the development of severe immunodeficiency are important to ensure that the low death rate from AIDS is sustained and potentially decreased even further[17].
Rates of death from non-AIDS cancer have remained stable over time, and is now the most common cause of non-AIDS deaths [1,15,16]. Although there is evidence that non-AIDS cancers are associated with immunodeficiency and potentially HIV infection itself[7,18], adjustment for CD4 cell count did not affect the association seen with calendar time (data not shown and [18]), and the same trends were seen even when only considering those with controlled viral replication. Two alternative potential explanations for this stable death rate are an increase in non-AIDS cancer rates over time, but with improved patient management and therefore better prognosis, or alternatively a stable incidence rate with similar prognosis over time. Previous work suggests the latter scenario is most likely[19]. The impact of specific antiretroviral drugs on non-AIDS cancer rates is currently unknown and requires further study, although recent findings show an increased risk of anal cancer with increasing exposure to protease inhibitors[20]. It is important to note that HIV-positive populations have a high prevalence of other risk factors, such as smoking, alcohol use, chronic viral hepatitis and other pro-oncogenic virus such as human papilloma virus (HPV)[21,22,34,35]. Reductions in the prevalence of these modifiable risk factors are likely required, along with early identification and improved management.
The finding of a stable rate of death from non-AIDS cancer in our study is of concern when contrasted to the experience in the general population, where death rates have decreased in the same time period[23,24] Although the spectrum of cancers may be very different, this suggests that any reduction in non-AIDS cancer death rates in the HIV-positive population will likely require more

widespread use of the various interventions that apparently have been successfully used in the general population.

We noted a decline in the rate of cardiovascular disease deaths during the study period of more than 65%, continuing the decline seen in earlier years in HIV-positive populations[14]. Although there has also been a decrease seen in the general population over the same time period, the magnitude of the reduction in the HIV-positive population seen here is of a substantially larger magnitude[25]. For example, in the European Region, age-standardised coronary heart disease death rates have fallen by less than 10%[25]. The decline observed in our study could not be attributed to changes over time in patient demographics, nor to changes in the CD4 cell count; indeed the percentage with hypertension, diabetes and high BMI increased over time. Furthermore, changes in the percentage with virological suppression did not explain the findings. This suggests that the decline could be a result of increased use of preventive interventions over the study period, such as smoking cessation, diet and exercise, lipid-lowering drugs and invasive procedures[26]. The observed reduction may also be as a result of better screening and earlier management, resulting in a reduction in CVD risk and incidence rates in later years. Furthermore, reduced utilisation of antiretrovirals traditionally associated with increased risk of CVD over the study period in favour of those with a better risk profile is also likely to have contributed to the observed decline. Awareness of potential associations between specific antiretrovirals with hyperlipidaemia (including protease inhibitors) and cardiovascular disease (including lopinavir and abacavir) has increased during the study period, and this is may have led to changes over time in targeted use of antiretrovirals according to cardiovascular risk profile[33].

There have been marked reductions in rates of liver-related deaths over the study period by more than 50%, continuing previously observed trends[1,27]. The number of liver-related deaths in individuals not co-infected with either HBV or HCV was very small, accounting for less than 5% of all liver-related deaths[28]. Thus, interventions to further reduce liver-related death should be targeted at the co-infected populations. Although much of the decline in death rates is likely attributable to the observed declines in the percentage with HBV or HCV, we observed that the trends in liver-related death were consistent when restricting analyses to co-infected individuals. Again, the reductions were not explained by changes over time in patient demographics in adjusted analyses. Furthermore, despite evidence that immunosuppression increases the risk of liver disease[7], reduction in rates of liver deaths over time could not be explained by changes in the CD4 cell count. The known anti-HBV activity of the antiretrovirals lamivudine, emtricitabine and tenofovir and their increased use over time has likely contributed to the observed decline. In contrast, effective treatment for HCV remained relatively uncommon during the study period. However, the introduction of the new anti-HCV protease inhibitors and other direct-acting antiviral drugs should make anti-HCV treatment substantially more effective in eradicating the infection and this may lead to further reductions in the death rate from this cause[29].

A previous D:A:D study showed an 11% increased incidence rate of liver-related death per additional year of overall ART use, after adjusting for current CD4 cell count[30]. It is possible that certain antiretroviral drugs that were used more frequently in the early part of the study period, such as didanosine and stavudine[31], may have adversely contributed to liver damage, an issue that we continue to explore.

Monitoring of trends over time in specific causes of death is only possible if every effort is made to ascertain the vital status of all study participants. All contributing study cohorts perform random monitoring of at least 10% of study participants' clinical records to ensure events are not missed. Careful ascertainment of cause of death is also imperative. Two recent studies demonstrated that large discrepancies in the assigned cause of death can occur according to the classification system used[1,32]. Therefore, initiatives such as the Coding Causes of Death in HIV project (CoDe) are vital[10]. This coding system enables consistency across HIV studies, accurate comparison of their findings, and also allows for cohort collaborations to examine rare causes of death[16].

Our study is observational, and so we cannot rule out the possibility or unmeasured confounding. Although every effort is taken to accurately classify deaths, there are occasions when insufficient documentation is available and they have to be classified as "unknown". Of 3909 deaths in this

study, 327 (8.4%) had available autopsy results. This highlights that autopsies can be a useful tool if the circumstances regarding a death are unclear. The wide geographical area covered helps to ensure the generalizability of the results, but if risk factors have varying importance in different settings some effects may be attenuated. Information on migrant status of study participants was not available. Finally, included individuals are from resource-rich countries, and results may not apply to other settings.
Life-long therapy with potent antiretrovirals means that monitoring numbers of deaths from specific causes that have to date been rare is vital. This will ensure that any increases are identified at an early stage. The results of our study demonstrate that currently there is no indication of any increase in risk of death from any specific cause as a potential result of long-term adverse effects of ART, and deaths from causes other than AIDS, CVD, liver and non-AIDS cancer remain low.

In summary, our study demonstrates that death rates have continued to decline amongst HIV-positive individuals over the past decade. Despite dramatic reductions in rates of AIDS-related deaths, this remains the most common cause. Non-AIDS cancer deaths are now the most common non-AIDS cause, and incidence rates have remained constant over time. In contrast, incidence rates of liver-related and CVD-related deaths have decreased, suggesting improvements in prevention and patient management of these conditions. Collection of specific causes of death in HIV is important to identify any emerging trends in the overall death rate, or from any unexpected specific cause to allow earlier interventions in HIV case management.

Putting research into context

Systematic review: A review of studies that have also investigated trends over time in specific causes of death was performed using the PubMed search engine. Mesh Search terms were used, including the terms “HIV”, “death” and “” in the time period 1999-2013 to ensure that studies were considering trends over time in the recent antiretroviral era. Selection of potential references was made by reading manuscript titles and abstracts, before reading the full paper of those deemed relevant through the initial search. Studies of trends over time in the general population were made through a PubMed search using each of the terms “cardiovascular death”, “liver death” and “cancer death” with “calendar time”.

What this study adds: This study has investigated the extent to which observed changes over time in cause-specific death rates can be attributed to concurrent changes in participant demographics, lifestyle factors, immunological status and presence co-morbidites such as HBV and HCV. Furthermore, it has investigated whether increases in numbers of deaths from specific causes that have to date been rare have occurred. This is vital to ensure that any increases are identified at an early stage and potential explanations, including antiretroviral-related toxicity, are investigated in a timely manner. Few studies of HIV positive individuals have sufficient sample sizes and detailed ascertainment of death to be able to address this question.

Conflicts of Interest

The D:A:D Study is funded by a grant from Highly Active Antiretroviral Therapy Oversight Committee (HAART-OC), a collaborative committee with representation from academic institutions, the European Agency for the Evaluation of Medicinal Products, the United States Food and Drug Administration, the patient community, and all pharmaceutical companies with licensed anti-HIV drugs in the European Union: Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals Inc., Bristol-Myers Squibb, Gilead Sciences Inc., Viiv Healthcare, Merck & Co Inc., Pfizer Inc, F. Hoffman-LaRoche Ltd and Janssen Pharmaceuticals.
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Legends for Figures
Figure 1 – Most common causes of death amongst HIV positive individuals, according to calendar year
Figure 2 – Age-standardised incidence rates for specific causes of deaths according to calendar year (a) Amongst entire D:A:D Study population; (b) Amongst follow-up time spent with viral load <400 copies/ml

Table 1 – Characteristics of study participants

		Characteristics at D:A:D Study entry		Characteristics of D:A:D participants under follow-up on:		
		All participants	**Died by last follow-up**	**1st January 2001**	**1st January 2006**	**1st January 2011**
Number		49731 (100%)	3909 (7.9%)	20863 (100%)	29497 (100%)	31938 (100%)
Gender	*Male*	36692 (73.8%)	3142 (8.6%)	15705 (75.3%)	21539 (73.0)	23502 (73.6)
Age (years)	*Median (IQR)*	38 (32, 45)	43 (37, 52)	39 (35, 46)	42 (37, 49)	46 (40, 53)
Mode of HIV acquisition	*IDU* *Heterosexual* *Other*[e] *MSM*	7628 (15.3%) 16167 (32.5%) 4025 (8.1%) 21911 (44.1%)	1159 (15.2%) 856 (5.3%) 385 (9.6%) 1509 (6.9%)	4350 (20.9%) 5654 (27.1%) 1580 (7.6%) 9279 (44.5%)	4535 (15.4) 9846 (33.4) 2201 (7.5) 12915 (43.8)	3859 (12.1) 11257 (35.3) 1984 (6.2) 14838 (46.5)
Known HCV positive[a]	*Yes*	6447 (13.0%)	920 (14.3%)	3562 (17.1%)	2676 (9.1)	1977 (6.2)
Known HBV positive[b]	*Yes*	5431 (10.9%)	581 (10.7%)	2387 (11.4%)	3059 (10.4)	2599 (8.1)
Smoking status	*Current* *Former* *Never* *Unknown*	17224 (34.6%) 8655 (17.4%) 12304 (24.7%) 11548 (23.2%)	1584 (9.2%) 753 (8.7%) 611 (45.0%) 961 (8.3%)	8880 (42.6%) 4062 (19.5%) 5109 (24.5%) 2812 (13.5%)	11716 (39.7) 6093 (20.7) 7215 (24.5) 4473 (15.2)	12077 (37.8) 7857 (24.6) 3967 (12.4) 8037 (25.2)
BMI (kg/m^2)	*Median (IQR)*	23.0 (21.0, 25.3); n=42908	22.3 (20.1, 24.7); n=3317	23.0 (21.1, 25.3) n=13191	23.2 (21.1, 25.7) n=21417	23.8 (21.5, 26.3) n=21003
Hypertension[c]	*Yes*	7863 (15.8%)	759 (9.7%)	2325 (11.1%)	6926 (23.5)	10176 (31.9)
Diabetes[d]	*Yes*	1362 (2.7%)	267 (19.6%)	368 (1.8%)	928 (3.2)	1470 (4.6)
Total cholesterol (mmol/l)	*Median (IQR)*	4.7 (4.0, 5.7); n=41603	4.7 (3.8, 5.7); n=3205	5.1 (4.2, 6.0) n=19207	4.9 (4.1, 5.7) n=27443	4.9 (4.2, 5.7) n=31253
Previous AIDS diagnosis	*Yes*	10482 (21.1%)	1484 (14.2%)	5316 (25.5%)	7888 (26.7)	8771 (27.5)
CD4 cell count ($cells/mm^3$)	*Median (IQR)*	400 (242, 590); n=48548	265 (111, 459); n=3799	446 (286, 644) n=20804	468 (320, 656) n=29338	547 (400, 727) n=31909
Currently on ART and Viral load <400 c/ml	*Yes*	20802/47449 (43.8%)[e]	1429/3699 (38.6%)[e]	10874 (52.1%)	17940 (60.8%)	25640 (80.3%)
Ever exposed to ART (years)	*n;* *Median (IQR)*	30430 (61.1%); 2.9 (1.2, 4.8)	2946 (9.7%); 3.7 (1.9, 5.7)	18120 (87%) 3.3 (1.9, 5.0)	24594 6.2 (3.1, 8.7)	29260 7.9 (3.6, 12.6)
Ever exposed to PI (years)	*n;* *Median (IQR)*	23072 (46.4%); 2.2 (1.0, 3.2)	2430 (10.5%); 2.5 (1.3, 3.4)	15008 (71.9%) 2.5 (1.4, 3.3)	19207 3.5 (1.6, 6.2)	21827 4.5 (2.0, 8.5)
Ever exposed to NNRTI (years)	*n;* *Median (IQR)*	14468 (29.1%); 1.0 (0.4, 1.8)	1413 (9.8%); 0.9 (0.4, 1.6)	8066 (38.7%) 0.9 (0.4, 1.4)	17048 2.5 (1.0, 4.4)	22256 3.5 (1.4, 6.9)

IQR=inter-quartile range; ART=antiretroviral therapy; PI=protease inhibitor; NNRTI=non nucleoside reverse transcriptase inhibitor; HBV=hepatitis B virus; HCV=hepatitis C virus; BMI=body mass index;c/ml=copies/ml
[a]HCV antibody positive; [b]HBsAg positive, HBeAg positive or HBV DNA positive/anti-Hbe positive;[c] Systolic blood pressure>140 mmHg; Diastolic blood pressure>90 Hg; or receiving anti-hypertensives; [d] Centrally validated endpoint: see www.cphiv.dk**;** [e]Viral load not available for all pre-study entry

Table 2 – Specific causes of death in the D:A:D Study, 1999-2011

	Number (%)
Total deaths	**3909 (100.0)**
AIDS-related	**1123 (28.7)**
Liver-related	**515 (13.2)**
Chronic viral hepatitis [a]	*447 (11.4)*
Liver failure	*68 (1.7)*
CVD-related	**436 (11.1)**
MI, definite or possible	*225 (5.9)*
Stroke	*56 (1.4)*
Other CVD	*60 (1.5)*
Other heart disease	*86 (2.2)*
Complications due to diabetes mellitus	*9 (0.2)*
Non-AIDS cancer [b]	**590 (15.1)**[c]
Other/Unknown	**1245 (31.8)**
Suicide	*150 (3.8)*
Drug overdose	*109 (2.8)*
Euthanasia	*16 (0.4)*
Homicide	*22 (0.6)*
Accident	*74 (1.9)*
Invasive bacterial infection	*259 (6.6)*
Lactic acidosis	*17 (0.4)*
Pancreatitis	*20 (0.5)*
Renal dysfunction/ disease	*48 (1.2)*
Other	*266 (5.8)*
Unknown	*264 (6.8)*

[a] Includes liver cancers as a result of viral hepatitis-related liver failure; [b] Includes lung cancers, prostate cancers, anal cancers, head- and neck cancers, Hodgkin's lymphomas, primary liver cancers (excluding hepatitis-related liver cancers, which are classified as "chronic viral hepatitis"), gastrointestinal cancers, breast cancers, uterus cancers, testicular cancers, penile cancers bladder cancers, kidney cancers, primary bone tumors, brain tumors (except non-Hodgkins´ lymphomas), unknown primary tumors and acute/chronic leukemias; [c] Most commonly reported cancers: lung (n=155), anal (38), head and neck (35), Hodgkins lymphoma (26)

Supplementary Table 3 – Unadjusted (crude) and age-standardised mortality incidence rates for specific causes of death over calendar time

		Incidence rate per 1000 person-years (95% confidence interval)					
	Total	**1999/2000**	**2001/2002**	**2003/2004**	**2005/2006**	**2007/2008**	**2009/2011**
Person-years follow-up	**308719**	**14661**	**46426**	**54530**	**59490**	**64572**	**69040**
All-cause							
N	3909	256	788	862	718	658	627
Unadjusted	12.7 (12.3, 13.1)	17.5 (15.3, 19.6)	17.0 (15.8, 18.2)	15.8 (14.8, 16.9)	12.1 (11.2, 13.0)	10.2 (9.4, 11.0)	9.1 (8.4, 9.8)
Age-standardised	12.2 (11.9, 12.6)	18.6 (16.3, 21.1)	17.6 (16.4, 18.9)	15.8 (14.8, 16.9)	11.6 (10.7, 12.4)	9.5 (8.8, 10.3)	8.0 (7.4, 8.7)
AIDS-related							
N	1123	87	250	278	195	172	141
Unadjusted	3.6 (3.4, 3.9)	5.9 (4.7, 7.2)	5.4 (4.7, 6.1)	5.1 (4.5, 5.7)	3.3 (2.8, 3.7)	2.7 (2.3, 3.1)	2.0 (1.7, 2.4)
Age-standardised	3.6 (3.4, 3.8)	6.0 (4.8, 7.5)	5.5 (4.9, 6.3)	5.1 (4.5, 5.7)	3.2 (2.8, 3.7)	2.7 (2.3, 3.1)	2.0 (1.7, 2.4)
Liver-related							
N	515	40	121	105	102	83	64
Unadjusted	1.7 (1.5, 1.8)	2.7 (1.9, 3.6)	2.6 (2.1, 3.1)	1.9 (1.6 2.3)	1.7 (1.4, 2.0)	1.3 (1.0, 1.5)	0.9 (0.7, 1.2)
Age-standardised	1.6 (1.5, 1.8)	2.9 (2.1, 4.0)	2.7 (2.2, 3.2)	1.9 (1.6 2.3)	1.7 (1.3, 2.0)	1.2 (0.9, 1.5)	0.8 (0.6, 1.1)
CVD-related							
N	436	26	90	97	84	79	60
Unadjusted	1.4 (1.3, 1.5)	1.8 (1.1, 2.5)	1.9 (1.5, 2.3)	1.8 (1.4, 2.1)	1.4 (1.1, 1.7)	1.2 (1.0, 1.5)	0.9 (0.6, 1.1)
Age-standardised	1.3 (1.2, 1.5)	2.0 (1.3, 2.9)	2.0 (1.6, 2.5)	1.8 (1.4, 2.1)	1.3 (1.0, 1.6)	1.1 (0.9, 1.4)	0.7 (0.5, 0.9)
Non-AIDS cancer[a]							
N	590	24	86	116	104	118	142
Unadjusted	1.9 (1.8, 2.1)	1.6 (1.0, 2.3)	1.9 (1.5, 2.2)	2.1 (1.7 2.5)	1.7 (1.4, 2.1)	1.8 (1.5, 2.2)	2.1 (1.7, 2.4)

Age-standardised	1.8 (1.6, 1.9)	1.9 (1.2, 2.8)	2.0 (1.6, 2.5)	2.1 (1.7 2.5)	1.6 (1.3, 2.0)	1.6 (1.3, 1.9)	1.6 (1.3, 1.9)
Other known							
N	981	68	207	218	184	149	155
Unadjusted	3.2 (3.0, 3.4)	4.6 (3.5, 5.7)	4.5 (3.9, 5.1)	4.0 (3.5, 4.5)	3.1 (2.6, 3.5)	2.3 (1.9, 2.7)	2.2 (1.9, 2.6)
Age-standardised	3.1 (2.9, 3.3)	5.0 (3.8, 6.4)	4.6 (4.0, 5.3)	4.0 (3.5, 4.5)	3.0 (2.6, 3.4)	2.2 (1.7, 2.4)	2.0 (1.7, 2.4)
Unknown							
N	264	11	34	48	49	57	65
Unadjusted	0.9 (0.8, 1.0)	0.8 (0.3, 1.2)	0.7 (0.5, 1.0)	0.9 (0.6, 1.1)	0.8 (0.6, 1.1)	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)
Age-standardised	0.8 (0.7, 0.9)	0.8 (0.4, 1.5)	0.7 (0.5, 1.0)	0.9 (0.6, 1.1)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)

CI=confidence interval; CVD=cardiovascular disease

95% CIs for unadjusted method calculated using a Normal approximation, unless there were fewer than 20 events, in which case the exact Poisson method was used. 95% CIs for age-standardised method calculated using Dobson's approach

[a] Includes lung cancers, prostate cancers, anal cancers, head- and neck cancers, Hodgkin's lymphomas, primary liver cancers (excluding hepatitis-related liver cancers, which are classified as "chronic viral hepatitis"), gastrointestinal cancers, breast cancers, uterus cancers, testicular cancers, penile cancers bladder cancers, kidney cancers, primary bone tumors, brain tumors (except non-Hodgkins´ lymphomas), unknown primary tumors and acute/chronic leukemias

Table 4–Incidence Rate ratios of underlying cause of death over calendar time

	Incidence Rate ratio (95% confidence interval) of death					
	1999/ 2000 (reference)	**2001/2002**	**2003/2004**	**2005/2006**	**2007/2008**	**2009-2011**
Total						
Unadjusted	1.0	0.97 (0.84, 1.12)	0.91 (0.79, 1.04)	0.69 (0.60, 0.80)	0.58 (0.51, 0.67)	0.52 (0.45, 0.60)
Adjusted [a]	1.0	1.07 (0.93, 1.23)	1.03 (0.90, 1.19)	0.81 (0.70, 0.94)	0.72 (0.62, 0.84)	0.72 (0.61, 0.83)
AIDS-related						
Unadjusted	1.0	0.91 (0.71, 1.16)	0.86 (0.68, 1.09)	0.55 (0.43, 0.71)	0.45 (0.35, 0.58)	0.34 (0.26, 0.45)
Adjusted [a]	1.0	1.11 (0.87, 1.42)	1.18 (0.92, 1.50)	0.85 (0.65, 1.10)	0.84 (0.64, 1.09)	0.92 (0.70, 1.22)
Adjusted, no CD4 [b]	1.0	1.09 (0.85, 1.40)	1.11 (0.87, 1.42)	0.75 (0.58, 0.98)	0.68 (0.52, 0.89)	0.63 (0.48, 0.84)
Liver-related						
Unadjusted	1.0	0.96 (0.67, 1.37)	0.71 (0.49, 1.02)	0.63 (0.44, 0.91)	0.47 (0.32, 0.69)	0.34 (0.23, 0.50)
Adjusted [a]	1.0	1.03 (0.71, 1.49)	0.81 (0.55, 1.18)	0.75 (0.51, 1.10)	0.61 (0.41, 0.91)	0.48 (0.32, 0.74)
CVD-related						
Unadjusted	1.0	1.09 (0.71, 1.69)	1.00 (0.65, 1.55)	0.80 (0.51, 1.24)	0.69 (0.44, 1.07)	0.49 (0.31, 0.78)
Adjusted [a]	1.0	1.02 (0.65, 1.59)	0.87 (0.56, 1.36)	0.64 (0.40, 1.00)	0.51 (0.32, 0.81)	0.33 (0.20, 0.53)
Non-AIDS cancer [c]						
Unadjusted	1.0	1.13 (0.72, 1.78)	1.30 (0.84, 2.02)	1.07 (0.69, 1.66)	1.12 (0.72, 1.73)	1.26 (0.82, 1.94)
Adjusted [a]	1.0	1.08 (0.68, 1.70)	1.18 (0.76, 1.85)	0.89 (0.56, 1.40)	0.90 (0.57, 1.41)	0.99 (0.63, 1.55)
Other/Unknown						
Unadjusted	1.0	0.96 (0.75, 1.24)	0.91 (0.70, 1.16)	0.73 (0.56, 0.94)	0.59 (0.46, 0.77)	0.59 (0.46, 0.76)
Adjusted [a]	1.0	1.07 (0.82, 1.38)	1.03 (0.80, 1.33)	0.86 (0.66, 1.12)	0.73 (0.56, 0.96)	0.77 (0.58, 1.01)

CVD=cardiovascular disease; Results from Poisson Regression Model

[a]Adjusted for gender, age, ethnicity, risk for HIV acquisition, HBV status, HCV status, smoking status, diabetes, hypertension, current HIV RNA viral load, current BMI and current CD4 cell count; [b] Model adjusted for factors listed in [a], except for current CD4 cell count, which was excluded from this model; [c] Includes lung cancers, prostate cancers, anal cancers, head- and neck cancers, Hodgkin's lymphomas, primary liver cancers (excluding hepatitis-related liver cancers, which are classified as "chronic viral hepatitis"), gastrointestinal cancers, breast cancers, uterus cancers, testicular cancers, penile cancers bladder cancers, kidney cancers, primary bone tumors, brain tumors (except non-Hodgkins´ lymphomas), unknown primary tumors and acute/chronic leukemias

Supplementary Table 5 – Unadjusted (crude) and age-standardised mortality incidence rates for specific causes of death over calendar time amongst those on antiretroviral therapy with viral load<50 copies/ml

		Incidence rate per 1000 person-years (95% confidence interval)					
	Total	**1999/2000**	**2001/2002**	**2003/2004**	**2005/2006**	**2007/2008**	**2009/2011**
Person-years follow-up	**194338**	**7158**	**25663**	**31306**	**63240**	**42616**	**51355**
All-cause							
N	1859	72	299	335	329	388	436
Unadjusted	9.6 (9.1, 10.0)	10.1 (7.7, 12.4)	11.7 (10.3, 13.0)	10.7 (9.6, 11.8)	9.1 (8.1, 10.1)	9.1 (8.2, 10.0)	8.5 (7.7, 9.3)
Age-standardised	12.2 (11.9, 12.6)	10.6 (8.3, 13.4)	11.6 (10.3, 13.0)	10.0 (8.9, 11.1)	8.0 (7.1, 8.9)	7.7 (6.9, 8.5)	6.7 (6.0, 7.4)
AIDS-related							
N	273	14	43	53	49	49	65
Unadjusted	1.4 (1.2, 1.6)	2.0 (1.1, 3.3)	1.7 (1.2, 2.2)	1.7 (1.2, 2.1)	1.4 (1.0, 1.7)	1.1 (0.8, 1.5)	1.3 (1.0, 1.6)
Age-standardised	1.3 (1.2, 1.5)	2.0 (1.1, 3.3)	1.7 (1.2, 2.2)	1.7 (1.2, 2.2)	1.3 (0.9, 1.7)	1.0 (0.7, 1.3)	1.1 (0.8, 1.4)
Liver-related							
N	263	12	55	46	51	53	46
Unadjusted	1.4 (1.2, 1.6)	2.0 (1.1, 3.3)	1.7 (1.6, 2.7)	1.5 (1.0, 1.9)	1.4 (1.0, 1.8)	1.2 (0.9, 1.6)	0.9 (0.6, 1.2)
Age-standardised	1.8 (0.9, 3.2)	1.8 (0.9, 3.2)	2.2 (1.6, 2.8)	1.4 (1.0, 1.9)	1.3 (0.9, 1.7)	1.1 (0.8, 1.4)	0.7 (0.5, 1.0)
CVD-related							
N	289	9	52	60	51	66	51
Unadjusted	1.5 (1.3, 1.7)	1.3 (0.6, 2.4)	2.0 (1.5, 2.6)	1.9 (1.4, 2.4)	1.4 (1.0, 1.8)	1.5 (1.2, 1.9)	1.0 (0.7, 1.3)
Age-standardised	1.3 (1.1, 1.4)	1.4 (0.6, 2.6)	2.0 (1.5, 2.7)	1.8 (1.3, 2.3)	1.1 (0.8, 1.5)	1.3 (1.0, 1.6)	0.7 (0.5, 1.0)
Non-AIDS cancer[a]							
N	401	10	46	74	58	93	120
Unadjusted	2.1 (1.9, 2.3)	1.4 (0.7, 2.6)	1.8 (1.3, 2.3)	2.4 (1.8 2.9)	1.6 (1.2, 2.0)	2.2 (1.7, 2.6)	2.3 (1.9, 2.8)
Age-standardised	1.7 (1.5, 1.9)	1.5 (0.7, 2.7)	1.8 (1.3, 2.4)	2.1 (1.7 2.7)	1.4 (1.0, 1.8)	1.8 (1.4, 2.2)	1.6 (1.3,

							1.9)
Other known							
N	489	21	91	81	99	90	107
Unadjusted	2.5 (2.3, 2.7)	2.9 (1.7, 4.2)	4.5 (3.9, 5.1)	3.5 (2.8, 4.3)	2.6 (2.0, 3.2)	2.7 (2.2, 3.3)	2.1 (1.7, 2.5)
Age-standardised	3.1 (2.9, 3.3)	3.1 (1.9, 4.7)	3.5 (2.8, 4.3)	2.4 (1.9, 3.0)	2.4 (2.0, 3.0)	1.9 (1.5, 2.3)	1.8 (1.4, 2.2)
Unknown							
N	144	6	12	21	21	37	47
Unadjusted	0.7 (0.6, 0.9)	0.8 (0.3, 1.8)	0.5 (0.2, 0.7)	0.7 (0.4, 1.0)	0.6 (0.3, 0.8)	0.9 (0.6, 1.1)	0.9 (0.7, 1.2)
Age-standardised	0.6 (0.5, 0.8)	0.9 (0.3, 2.0)	0.5 (0.2, 0.8)	0.6 (0.4, 0.9)	0.5 (0.3, 0.8)	0.7 (0.5, 1.0)	0.8 (0.5, 1.0)

CI=confidence interval; CVD=cardiovascular disease

95% CIs for unadjusted method calculated using a Normal approximation, unless there were fewer than 20 events, in which case the exact Poisson method was used. 95% CIs for age-standardised method calculated using Dobson's approach. Estimates are age-standardised to entire D:A:D population

[a] Includes lung cancers, prostate cancers, anal cancers, head- and neck cancers, Hodgkin's lymphomas, primary liver cancers (excluding hepatitis-related liver cancers, which are classified as "chronic viral hepatitis"), gastrointestinal cancers, breast cancers, uterus cancers, testicular cancers, penile cancers bladder cancers, kidney cancers, primary bone tumors, brain tumors (except non-Hodgkins´ lymphomas), unknown primary tumors and acute/chronic leukemias

Supplementary Table 6 – Incidence Rate Ratios (RRs) of underlying cause of death over calendar time amongst those on antiretroviral therapy with viral load<50 copies/ml

	Incidence Rate ratio (95% confidence interval) of death					
	1999/ 2000 (reference)	**2001/2002**	**2003/2004**	**2005/2006**	**2007/2008**	**2009-2011**
Total						
Unadjusted	1.0	1.16 (0.90, 1.50)	1.06 (0.82, 1.37)	0.90 (0.70, 1.16)	0.91 (0.70, 1.16)	0.84 (0.66, 1.08)
Adjusted [a]	1.0	1.24 (0.95, 1.61)	1.10 (0.84, 1.43)	0.87 (0.66, 1.13)	0.84 (0.65, 1.09)	0.80 (0.62, 1.04)
AIDS-related						
Unadjusted	1.0	0.86 (0.47, 1.57)	0.87 (0.48, 1.56)	0.69 (0.38, 1.25)	0.59 (0.32, 1.06)	0.65 (0.36, 1.15)
Adjusted [a]	1.0	0.98 (0.53, 1.82)	1.02 (0.56, 1.83)	0.79 (0.43, 1.46)	0.67 (0.36, 1.23)	0.89 (0.49, 1.63)
Adjusted, no CD4 [b]	1.0	0.91 (0.49, 1.68)	0.84 (0.46, 1.54)	0.65 (0.35, 1.21)	0.53 (0.29, 0.99)	0.56 (0.31, 1.03)
Liver-related						
Unadjusted	1.0	1.28 (0.68, 2.39)	0.88 (0.46, 1.65)	0.84 (0.45, 1.57)	0.74 (0.40, 1.39)	0.53 (0.28, 1.01)
Adjusted [a]	1.0	1.44 (0.75, 2.74)	1.01 (0.52, 1.97)	0.95 (0.49, 1.84)	0.87 (0.45, 1.68)	0.67 (0.34, 1.32)
CVD-related						
Unadjusted	1.0	1.61 (0.79, 3.27)	1.52 (0.76, 3.07)	1.12 (0.55, 2.27)	1.23 (0.61, 2.47)	0.79 (0.39, 1.60)
Adjusted [a]	1.0	1.52 (0.74, 3.12)	1.27 (0.62, 2.60)	0.82 (0.39, 1.69)	0.82 (0.40, 1.68)	0.49 (0.23, 1.02)
Non-AIDS cancer [c]						
Unadjusted	1.0	1.28 (0.65, 2.54)	1.69 (0.87, 3.27)	1.15 (0.59, 2.24)	1.56 (0.81, 3.00)	1.67 (0.88, 3.19)
Adjusted [a]	1.0	1.30 (0.65, 2.59)	1.59 (0.81, 3.12)	0.96 (0.49, 1.89)	1.24 (0.64, 2.42)	1.34 (0.69, 2.60)
Other/Unknown						
Unadjusted	1.0	1.06 (0.70, 1.63)	0.86 (0.57, 1.32)	0.88 (0.58, 1.33)	0.79 (0.52, 1.20)	0.80 (0.53, 1.20)
Adjusted [a]	1.0	1.15 (0.74,	0.90 (0.58,	0.87 (0.56,	0.76 (0.49,	0.75 (0.49,

	1.77)	1.40)	1.34)	1.18)	1.16)	

CVD=cardiovascular disease; Results from Poisson Regression Model

[a]Adjusted for gender, age, ethnicity, risk for HIV acquisition, HBV status, HCV status, smoking status, diabetes, hypertension, current HIV RNA viral load, current BMI and current CD4 cell count; [b] Model adjusted for factors listed in [a], except for current CD4 cell count, which was excluded from this model; [c] Includes lung cancers, prostate cancers, anal cancers, head- and neck cancers, Hodgkin's lymphomas, primary liver cancers (excluding hepatitis-related liver cancers, which are classified as "chronic viral hepatitis"), gastrointestinal cancers, breast cancers, uterus cancers, testicular cancers, penile cancers bladder cancers, kidney cancers, primary bone tumors, brain tumors (except non-Hodgkins´ lymphomas), unknown primary tumors and acute/chronic leukemia