Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration

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Summary

Background With the advent of effective antiretroviral treatment, the life expectancy for people with HIV is now approaching that seen in the general population. Consequently, the relative importance of other traditionally non-AIDS-related morbidities has increased. We investigated trends over time in all-cause mortality and for specific causes of death in people with HIV from 1999 to 2011.

Methods Individuals from the Data collection on Adverse events of anti-HIV Drugs (D:A:D) study were followed up from March, 1999, until death, loss to follow-up, or Feb 1, 2011, whichever occurred first. The D:A:D study is a collaboration of 11 cohort studies following HIV-1-positive individuals receiving care at 212 clinics in Europe, USA, and Australia. All fatal events were centrally validated at the D:A:D coordinating centre using coding causes of death in HIV (CoDe) methodology. We calculated relative rates using Poisson regression.

Findings 3909 of the 49 731 D:A:D study participants died during the 308 719 person-years of follow-up (crude incidence mortality rate, 12·7 per 1000 person-years [95% CI 12·3–13·1]). Leading underlying causes were: AIDS-related (1123 [29%] deaths), non-AIDS-defining cancers (590 [15%] deaths), liver disease (515 [13%] deaths), and cardiovascular disease (436 [11%] deaths). Rates of all-cause death per 1000 person-years decreased from 17·5 in 1999–2000 to 9·1 in 2009–11; we saw similar decreases in death rates per 1000 person-years over the same period for AIDS-related deaths (5·9 to 2·0), deaths from liver disease (2·7 to 0·9), and cardiovascular disease deaths (1·8 to 0·9). However, non-AIDS cancers increased slightly from 1·6 per 1000 person-years in 1999–2000 to 2·1 in 2009–11 (p=0·58). After adjustment for factors that changed over time, including CD4 cell count, we detected no decreases in AIDS-related death rates (relative rate for 2009–11 *vs* 1999–2000: 0·92 [0·70–1·22]). However, all-cause (0·72 [0·61–0·83]), liver disease (0·48 [0·32–0·74]), and cardiovascular disease (0·33 [0·20–0·53) death rates still decreased over time. The percentage of all deaths that were AIDS-related (87/256 [34%] in 1999–2000 and 141/627 [22%] in 2009–11) and liver-related (40/256 [16%] in 1999–2000 and 64/627 [10%] in 2009–11) decreased over time, whereas non-AIDS cancers increased (24/256 [9%] in 1999–2000 to 142/627 [23%] in 2009–11).

Interpretation Recent reductions in rates of AIDS-related deaths are linked with continued improvement in CD4 cell count. We hypothesise that the substantially 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.

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Introduction

In settings with access to antiretroviral therapy (ART), AIDS-related mortality in HIV-positive individuals in care has decreased substantially, 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 has increased, and a wider range of complications has been seen than in previous years.[1]

The occurrence of some non-AIDS-related morbidities might be higher in people with HIV than in the general population for three main reasons. First, the HIV-positive population in high-income settings has a high level of traditional risk factors for non-AIDS morbidities, such as smoking and hepatitis co-infection.[4–6] Second, available evidence suggests that the persistent immunodeficiency, immune dysregulation, immune activation, and inflammation associated with HIV infection, including in patients on ART, might increase the risk of some of these morbidities.[7,8] Third, antiretroviral-related adverse events such as dyslipidaemia and diabetes might also play a part. Although ART has clear benefits, lifelong exposure to these drugs is likely to be needed. Thus, long-term surveillance for emerging or not-yet-identified serious adverse events caused by extended exposure to these novel agents is important. The reporting of such

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See Online for appendix

For more on **centrally validated endpoint** see http://www.cphiv.dk/Ongoing-Studies/DAD/Study-Documents

events using a passive, clinician-initiated approach will probably not be sensitive enough to detect emerging issues should they occur. A major aim of the Data collection on Adverse events of anti-HIV Drugs (D:A:D) study is to identify whether emerging serious toxicities are linked with use of ART by looking for increases in the rates of mortality either from a particular organ system, from cancers, or from other as-yet unanticipated causes.

We aimed to investigate trends over time in all-cause mortality and for specific causes of death from 1999 to 2011 within the D:A:D study. We examined whether any recorded changes over time in death rates (overall and cause-specific) could 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

Study design

Participants included were from the D:A:D study,[9] a collaboration of 11 (nine ongoing) cohort studies of 49 731 individuals with HIV-1 receiving care at 212 clinics in Europe, USA, and Australia. All participants were under active follow-up in their cohorts at the time of enrolment. Prospective follow-up, with visits of at least every 8 months, began in January, 1999, irrespective of ART status. Participants were recruited during three recruitment waves: December, 1999–April, 2001; December, 2003, to May, 2004; and January–December, 2010. All clinical outcomes, including deaths, are reported in real time by the cohorts to the D:A:D coordinating centre for validation and classification. For 84% of all reported deaths, the sites provided a completed case report form and so the cause of death could be centrally

	Characteristics at study entry		Characteristics at follow-up visits		
	All participants	Died by last follow-up	Jan 1, 2001	Jan 1, 2006	Jan 1, 2011
Number of participants	49 731 (100%)	3909 (8%)	20 863 (100%)	29 497 (100%)	31 938 (100%)
Men	36 692 (74%)	3142 (9%)	15 705 (75%)	21 539 (73%)	23 502 (74)
Age in years	38 (32–45)	43 (37–52)	39 (35–46)	42 (37–49)	46 (40–53)
Mode of HIV acquisition					
Injection drug use	7628 (15%)	1159 (15%)	4350 (21%)	4535 (15%)	3859 (12%)
Heterosexual intercourse	16 167 (33%)	856 (5%)	5654 (27%)	9846 (33%)	11 257 (35%)
Other¶	4025 (8%)	385 (10%)	1580 (8%)	2201 (7%)	1984 (6%)
Sex between men	21 911 (44%)	1509 (7%)	9279 (44%)	12 915 (44%)	14 838 (46%)
Known HCV-positive*	6447 (13%)	920 (14%)	3562 (17%)	2676 (9%)	1977 (6%)
Known HBV-positive†	5431 (11%)	581 (11%)	2387 (11%)	3059 (10%)	2599 (8%)
Smoking status					
Current	17 224 (35%)	1584 (9%)	8880 (43%)	11 716 (40%)	12 077 (38%)
Former	8655 (17%)	753 (9%)	4062 (20%)	6093 (21%)	7857 (25%)
Never	12 304 (25%)	611 (5%)	5109 (25%)	7215 (24%)	3967 (12%)
Unknown	11 548 (23%)	961 (8%)	2812 (14%)	4473 (15%)	8037 (25%)
Body-mass index (kg/m^2; median [IQR]; n)	23·0 (21·0–25·3); 42 908	22·3 (20·1–24·7); 3317	23·0 (21·1–25·3); 13 191	23·2 (21·1–25·7); 21 417	23·8 (21·5–26·3); 21 003
Hypertension‡	7863 (16%)	759 (10%)	2325 (11%)	6926 (23%)	10 176 (32%)
Diabetes§	1362 (3%)	267 (20%)	368 (2%)	928 (3%)	1470 (5%)
Total cholesterol (mmol/L; median [IQR]; n)	4·7 (4·0–5·7); 41 603	4·7 (3·8–5·7); 3205	5·1 (4·2–6·0); 19 207	4·9 (4·1–5·7); 27 443	4·9 (4·2–5·7); 31 253
Previous AIDS diagnosis	10 482 (21 %)	1484 (14 %)	5316 (26%)	7888 (27%)	8771 (27%)
CD4 cell count (cells per mm; median [IQR]; n)	400 (242–590); 48 548	265 (111–459); 3799	446 (286–644); 20 804	468 (320–656); 29 338	547 (400–727) 31 909
Viral load <400 copies per mL (n/N [%])	20 802/47 449 (44%)¶	1429/3699 (39%)¶	11 447/19 430 (59%)	19 036/28 107 (68%)	26 236/31 628 (83%)
Ever exposed to ART (n [%]; median years [IQR])	30 430 (61%); 2·9 (1·2–4·8)	2946 (10%); 3·7 (1·9–5·7)	18 120 (87%); 3·3 (1·9–5·0)	24 594 (83%); 6·2 (3·1–8·7)	29 260 (92%); 7·9 (3·6–12·6)
Ever exposed to PI (n [%]; median years [IQR])	23 072 (46%); 2·2 (1·0–3·2)	2430 (11%); 2·5 (1·3–3·4)	15 008 (72%); 2·5 (1·4–3·3)	19 207 (65%); 3·5 (1·6–6·2)	21 827 (68%); 4·5 (2·0–8·5)
Ever exposed to NNRTI (n [%]; median years [IQR])	14 468 (29%); 1·0 (0·4–1·8)	1413 (10%); 0·9 (0·4–1·6)	8066 (39%) 0·9 (0·4–1·4)	17 048 (58%); 2·5 (1·0–4·4)	22 256 (70%); 3·5 (1·4–6·9)

Data are n (%) unless otherwise specified. HBV=hepatitis B virus. HCV=hepatitis C virus. PI=protease inhibitor. NNRTI=non-nucleoside reverse-transcriptase inhibitor. *HCV antibody positive. †HBsAg-positive, HBeAg-positive, or HBV DNA positive or anti-Hbe positive. ‡Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or receiving anti-hypertensives. §Centrally validated endpoint (see http://www.cphiv.dk/Ongoing-Studies/DAD/Study-Documents). ¶Viral load not available for all before study entry.

Table 1: **Characteristics of study participants**

validated. We used consistent classification categories for causes of death during the study period using adapted International Classification of Diseases (ICD)-10 codes, with the Cause of Death form used from 2004 onwards.[10]

Although data for both the underlying and other contributing causes of death were available, we assessed only the underlying cause, referring to it as the cause of death hereafter. For analysis, we grouped causes into the following five categories: AIDS related; cardiovascular disease related; liver disease related; non-AIDS cancers (ie, excluding Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer); and other or unknown.

All participating cohorts followed local national guidelines or regulations regarding patient consent and ethical review. In particular, of the countries represented by the participating cohorts, only Switzerland and Australia require specific ethical approval for D:A:D in addition to that required for their national cohorts (Swiss HIV Cohort Study and the Australian HIV Observational Database), both of which have obtained this approval.

Statistical analysis

We followed up individuals from study entry until 6 months after last clinic visit, until Feb 1, 2011, or death, whichever occurred first. Although follow-up was available until Feb 1, 2012, we excluded the last year to account for under-ascertainment due to delayed reporting.

We estimated crude and age-standardised (adjusted to the age distribution of the cohort in 2003–04, using Dobson's approach to calculate corresponding confidence intervals[11]) death incidence rates for each 2-year follow-up period. We calculated unadjusted and adjusted relative rates (RRs) for the association of calendar time with all-cause and cause-specific mortality using Poisson regression. We adjusted for both fixed-time variables—age at study entry (per 5 years older), sex, ethnic origin (white, black, or other), mode of HIV acquisition (sex between men, heterosexual intercourse, intravenous drug use, or other or unknown)—and time-updated variables—hepatitis B virus status (yes, no, or unknown; defined as HBsAg positive, HBeAg positive, or hepatitis B virus DNA positive or anti-Hbe positive), hepatitis C virus status (yes, no, or unknown; defined as HCVAb positive), smoking status (current, former, ex-smoker, or unknown), diabetes (yes or no; centrally validated endpoint), hypertension (yes or no; defined as systolic blood pressure >140 mm Hg; diastolic blood pressure >90 mm Hg, or receiving anti-hypertensives), HIV RNA viral load (on ART with viral load <400 copies per mL, on ART with viral load ≥400 copies per mL, off ART with viral load <10 000 copies per mL, or off ART with viral load ≥10 000 copies per mL), body-mass index (<18 kg/m², 18 kg/m² to ≤26 kg/m², >26 kg/m² to ≤30 kg/m², or >30 kg/m²), and CD4 cell count (per 50 cells per mm³).

We repeated all analyses, restricting to the person-years of follow-up in which study participants had a viral load of less than 400 copies per mL. We did these repeated analyses to investigate trends over time in death rates in those with an optimum response to ART.

We remodelled all multivariable Poisson regression models without adjusting for viral load. Next, because 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. We investigated the presence of these competing risks by excluding individuals from the cause-specific analyses if they died from other causes.[12] We remodelled all analyses according to the following demographic sub-groups: hepatitis B virus status, hepatitis C virus status, sex, HIV acquisition risk, smoking status, body-mass index, and age group. Analyses were also remodelled sequentially using multiple imputation to account for unknown causes of death, following the standard approach,[13] and, finally, remodelled stratified by wave of recruitment. We used SAS (version 9.3) for all statistical analyses.

For more on **Cause of Death form** see http://ww.cphiv.dk/Tools-Standards/CoDe

	Number of deaths (%)
Total deaths	3909 (100%)
AIDS-related	1123 (29%)
Liver-related	515 (13%)
Chronic viral hepatitis*	447 (11%)
Liver failure	68 (2%)
CVD-related	436 (11%)
Myocardial infarction, definite or possible	225 (6%)
Stroke	56 (1%)
Other CVD	60 (2%)
Other heart disease	86 (2%)
Complications due to diabetes	9 (<0·5%)
Non-AIDS cancer†	590 (15%)‡
Other or unknown	1245 (32%)
Suicide	150 (4%)
Drug overdose	109 (3%)
Euthanasia	16 (<0·5%)
Homicide	22 (1%)
Accident	74 (2%)
Invasive bacterial infection	259 (7%)
Lactic acidosis	17 (<0·5%)
Pancreatitis	20 (1%)
Renal dysfunction disease	48 (1%)
Other	266 (6%)
Unknown	264 (7%)

CVD=cardiovascular disease. *Includes liver cancers as a result of viral hepatitis-related liver failure. †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 tumours, brain tumours (except non-Hodgkin lymphomas), unknown primary tumours, and acute or chronic leukaemia. ‡Most commonly reported cancers: lung (n=155), anal (n=38), head and neck (n=35), and Hodgkin's lymphoma (n=26).

Table 2: **Specific causes of death, 1999–2011**

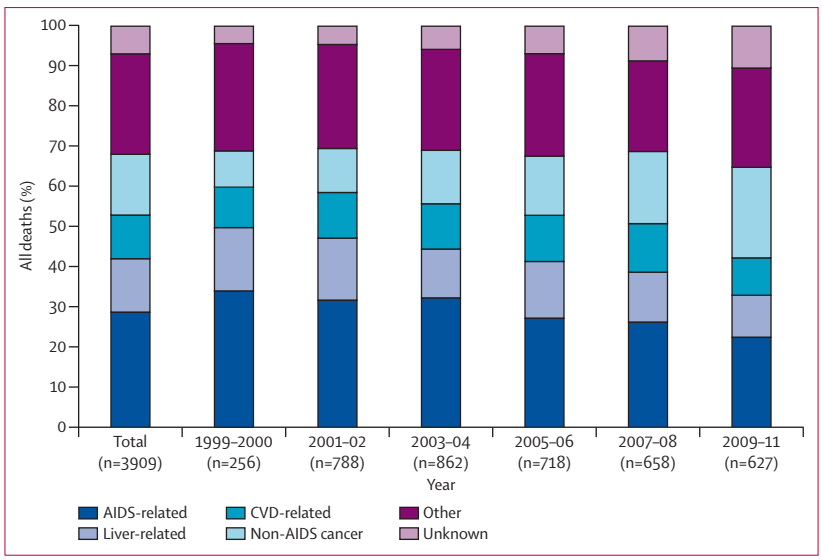

Figure 1: **Most common causes of death in people with HIV**
CVD=cardiovascular disease.

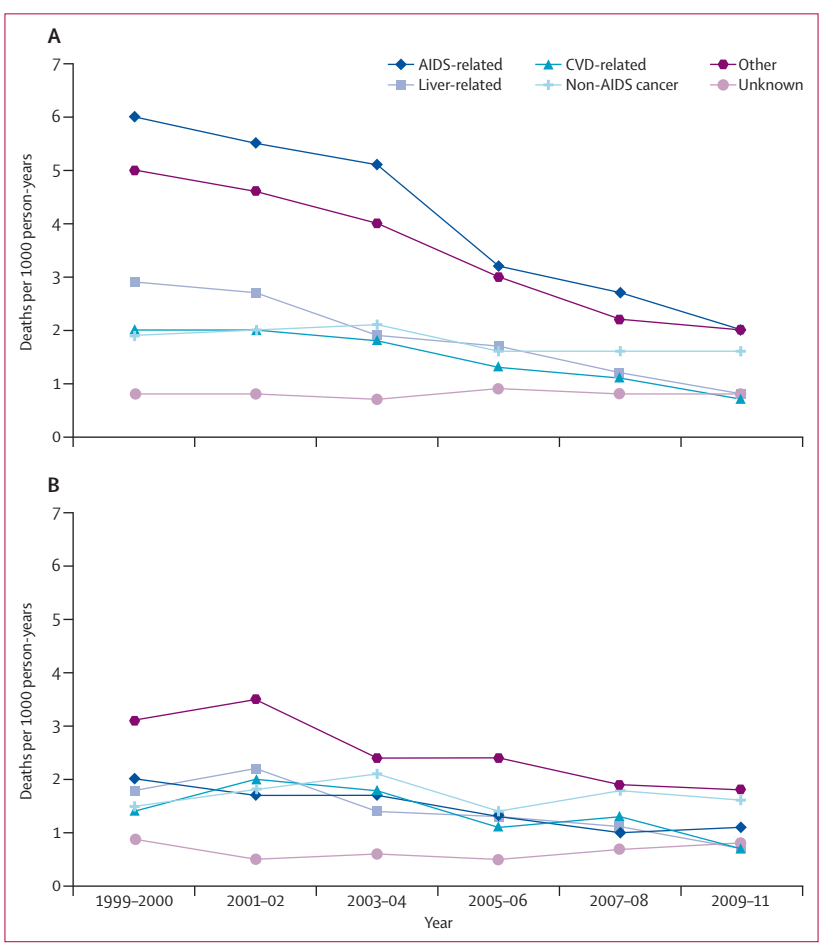

Figure 2: **Age-standardised incidence rates for specific causes of deaths**
(A) In entire D:A:D study population. (B) In individuals with a current viral load of less than 400 copies per mL during follow-up. CVD=cardiovascular disease.

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 had responsibility for submission for publication.

Results

Most of the 49731 D:A:D study participants were men, the most common mode of HIV acquisition was sex between men, and the median age at study entry was 38 years (table 1). Compared with participants who were being followed up on Jan 1, 2001 (when the first wave of recruitment was nearing completion), those who were being followed up in 2011 were less likely to have acquired HIV through intravenous drug use, less likely to be hepatitis B virus-positive or hepatitis C virus-positive, less likely to be a smoker, and more likely to have hypertension or diabetes (table 1). Those still in follow-up in 2011 were also more likely to be successfully treated on ART (with viral load <400 copies per mL), had a higher median CD4 count and a longer median length of time spent on ART (table 1).

3909 people died during the study period. Compared with the general D:A:D population, we recorded a higher proportion of deaths in men, hepatitis C virus-positive people, people with an intravenous drug use risk for HIV acquisition, smokers and individuals with a previous AIDS diagnosis, and the median CD4 cell count at study entry was lower than in the entire D:A:D study population (table 1).

The most common causes of death were AIDS-related causes, followed by non-AIDS-related cancers, liver disease, and cardiovascular disease (table 2). The most common causes of death listed as other were invasive bacterial infection, suicide, and drug overdose. Although it has remained the most common cause over the whole follow-up period, the percentage of all deaths attributable to AIDS decreased from 34% in 1999–2000 to 22% in 2009–11 ($p<0·0001$, χ^2 test; figure 1). The percentage of liver-related deaths also fell over the same period (16% to 10%). However, the proportion of all deaths that were from non-AIDS cancers increased (9% to 23%), making it the joint leading non-AIDS cause of death with AIDS-related deaths.

The 3909 deaths occurred over 308719 person-years of follow-up (median 5·8 person-years; IQR 3·3–9·9), corresponding to a crude incidence mortality rate of 12·7 per 1000 person-years (95% CI 12·3–13 ·1). The rate of death has decreased from 17·5 per 1000 person-years in 1999–2000 to 9·1 in 2009–11. This decrease in overall death rate remains after accounting for an ageing population through use of age-standardised estimates (figure 2; appendix). Similarly, we saw decreases in deaths related to AIDS, liver disease, and cardiovascular disease. The rate of non-AIDS cancer deaths, however, remained relatively constant, at 1·6 per 1000 person-years

in 1999–2000 and 2·1 per 1000 person-years in 2009–11. This information was also shown in the unadjusted rate ratios (table 3).

After adjusting for both fixed-time and time-updated confounders, the rate of all-cause mortality still decreased (table 3), which suggests that changes in these factors could not explain the decrease in death rates seen over time. Similarly, liver disease and cardiovascular death rates were substantially reduced in later years, even after accounting for changes in demographic factors over time. However, changes in factors over time did explain much of the recorded decrease in AIDS-related deaths, because the adjusted RRs in table 3 all approached one. Much of this confounding in AIDs-related death rate 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 might have changed over time did not affect the pattern for non-AIDS cancers, with rates remaining constant over the follow-up period.

In individuals with a viral load of less than 400 copies per mL, 1859 people died over 194 338 person-years of follow-up. As expected, the overall death rate was much lower in these individuals (9·6 per 1000 person-years; 95% CI 9·1–10·0) than it was in the general D:A:D population, particularly from AIDS-related causes (1·4 deaths per 1000 person-years; 1·2–1·6). Age-adjusted and crude death rates from each specific cause over time are shown in figure 2 and the appendix. Our study had lower statistical power to explore trends over time in this subgroup, but we saw no evidence of different trends than those seen in the main analysis. Furthermore, analysis of the adjusted rate ratios for changes in over time (appendix) showed no evidence of an increasing trend from any cause, although 95% CIs were wider than in the main analysis.

Results of the Poisson regression models, and calculation of incidence rates, were consistent in all sensitivity analyses done, including the results of multiple imputation (data not shown).

Discussion

Our findings suggest that death rates in HIV-positive individuals with access to care and antiretroviral therapy have decreased since 1999–2000. We can detect no indication of an increase in risk of death from any specific cause as a potential result of long-term adverse effects of ART, and the risk of death from other causes—ie, those other than AIDS-related disease, cardiovascular disease, liver disease, and non-AIDS cancers—is low. These findings provide further evidence of the substantial net benefits of ART.

Deaths due to most causes seemed to decrease over the study period, even after accounting for any effects of uncontrolled HIV replication, immunological

	1999–2000 (reference)	2001–02	2003–04	2005–06	2007–08	2009–11
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*	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*	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)†	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*	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*	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						
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*	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 or 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*	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)

Data are incidence rate ratio (95% CI) of death. CVD=cardiovascular disease. *Adjusted for sex, age, ethnic origin, risk for HIV acquisition, hepatitis B virus status, hepatitis C virus status, smoking status, diabetes, hypertension, current HIV RNA viral load, current body-mass index, and current CD4 cell count. †Model adjusted for all factors except for current CD4 cell count, which was excluded from this model.

Table 3: **Incidence rate ratios of underlying cause of death, by year**

***Panel:* Research in context**

Systematic review

We searched PubMed with the Mesh Search terms "HIV" and "cause of death" to identify original research articles published in English between Jan 1, 2001, and Dec 31, 2013, that investigated trends over time in specific causes of death in HIV-positive populations. Three studies in particular, by Helleberg and colleagues,[14] the Antiretroviral Cohort Collaboration,[16] and Simard and colleagues[15] considered specific causes of death during 1995–2008, 1996–2006, and 1980–2006 in large populations. These studies have shown that an overall decrease in death rates in HIV-positive populations have continued over time.[1,14,16] However, AIDS-related deaths remain the most common cause of death,[16] and non-AIDS-related cancers are now the most common non-AIDS cause of death.[1,15,16] Decreases have been seen over time in deaths from cardiovascular disease[14] and liver-related illnessed.[1,17]

Interpretation

The D:A:D Study is a large international study that has centralised and validated monitoring of causes of death. Our findings add to available evidence, showing that the improvements seen over time in deaths from AIDS-related causes can be explained by changes in the CD4 cell count. However, the decreases seen in the study period in the rate of deaths from cardiovascular disease and liver-related events cannot be explained by changes in immunological function or measured demographical factors, suggesting improved clinical management over time. Finally, rates of death from non-AIDS-related cancers have remained stable over time, suggesting further interventions in this area are necessary. The large study sample size and close monitoring enables surveillance for any other emerging trends in causes of unexpected deaths over time. Encouragingly, we detected no such trend.

improvements as measured by the CD4 count, and age. These findings are evident on analysis of the adjusted rate ratios (table 3) and the subgroup analysis in participants with a viral load of less than 400 copies per mL (appendix). However, that the overall rate in non-AIDS cancers has remained constant over time is concerning, and suggests that this is an important area that needs further research.

Findings from many studies of HIV-positive populations have shown pronounced decreases in AIDS-related deaths over time (panel).[1,14–17] That these improvements have continued into the most recent time period—ie, from 2001 onwards—is encouraging. The decrease in mortality could be largely explained by increases in CD4 cell counts in the study population, which were most likely a result of successful ART rather than changes in included participants over time in view of the fact that our findings were consistent when stratifying by recruitment wave. Any residual improvements not explained by the CD4 cell count might be due to better management of AIDS-related disorders and increased use of prophylactic treatments. However, despite all the improvements in AIDS-related morbidity, AIDS-related disease 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.[18]

Rates of death from non-AIDS-related cancers have remained stable over time, and these types of cancers are now the most common cause of non-AIDS deaths in people with HIV.[1,15,16] Although evidence exists that non-AIDS cancers are associated with immunodeficiency and potentially HIV infection itself,[7,19] adjustment for CD4 cell count in our study did not affect the association seen with calendar time (data not shown in our study), 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 management of patients and therefore better prognosis, or a stable incidence rate with similar prognosis over time, which findings from previous studies suggest to be most likely.[20] The effect of specific antiretroviral drugs on fatal and non-fatal non-AIDS cancer rates is unknown and needs further study, although findings from one study show an increased risk of anal cancer with increasing exposure to protease inhibitors.[21] HIV-positive populations have a high prevalence of other risk factors, such as smoking, alcohol use, chronic viral hepatitis, and other pro-oncogenic viruses such as human papilloma virus.[22–25] Reductions in the prevalence of these modifiable risk factors are probably needed, 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 compared with the experience in the general population, in which death rates have decreased over the same time period.[26,27] Although the spectrum of cancers might be very different, this finding suggests that any reduction in the number of deaths due to non-AIDS-related cancers in the HIV-positive population will probably require a more widespread use of the various interventions that have been successfully used in the general population.

We saw a decrease in the occurrence of deaths due to cardiovascular disease during the study period of more than 65%, continuing the decrease seen in earlier years (1996–99) in HIV-positive populations.[14] Although deaths from cardiovascular diseases have also decreased in the general population over the same period, the reduction in the HIV-positive population seen here is substantially larger than that seen in the general population.[28] For example, in the WHO European region, age-standardised coronary heart disease death rates in the general population have fallen by less than 10% during the past decade.[28] The fall seen 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 body-mass index increased over time. Furthermore, changes in the percentage with virological suppression did not explain the findings, suggesting that the decrease 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.[29] The reduction might also be a result of better screening and earlier management, resulting in a reduction in

cardiovascular disease risk and incidence rates. Furthermore, reduced use of antiretrovirals traditionally associated with increased risk of cardiovascular disease over the study period in favour of those with a better risk profile is also likely to have contributed to the decrease. 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 might have led to changes over time in targeted use of antiretrovirals according to cardiovascular risk profile.[30]

The occurrence of liver-related deaths over the study period decreases substantially (by more than 50%), continuing previously seen trends from studies stretching back as far as from 1992 onwards.[1,17] The number of liver-related deaths in individuals not co-infected with either hepatitis B virus or hepatitis C virus was very small, accounting for less than 5% of all liver-related deaths.[31] Thus, interventions to further reduce liver-related deaths should be targeted at these co-infected populations. Although much of the fall in death rates is probably attributable to the decreases in the percentage of participants with hepatitis B virus or hepatitis C virus, 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 activity against hepatitis B virus of the antiretrovirals lamivudine, emtricitabine, and tenofovir, and their increased use over time, has probably contributed to the decrease. By contrast with these antiretrovirals, effective treatment for hepatitis C virus remained uncommon during the study period. However, the introduction of the new protease inhibitors against hepatitis C virus and other direct-acting antiviral drugs should make hepatitis C virus treatment substantially more effective in eradicating the infection, which might lead to further reductions in the death rate from this cause.[32]

Findings from a previous D:A:D study showed an 11% increased incidence of liver-related deaths per additional year of overall ART use, after adjusting for current CD4 cell count.[33] However, some antiretroviral drugs that were used more frequently in the early part of the study period, such as didanosine and stavudine,[34] could 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. Investigators in all contributing cohort studies do 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. Large discrepancies in the assigned cause of death can occur according to the classification system used.[1,35] Therefore, initiatives such as the Coding Causes of Death in HIV project (CoDe) are crucial.[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 of unmeasured confounding. Although we made every effort to accurately classify deaths, there were occasions when insufficient documentation was available and deaths were classified as unknown. Of 3909 deaths in this study, 327 (8%) had available autopsy results. This finding draws attention to the fact that autopsies can be a useful procedure if the circumstances regarding a death are unclear. The wide geographical area covered in our study helps to ensure the generalisability of the results, but if risk factors have varying importance in different settings some effects might be attenuated. Information about migrant status of study participants was not available. Finally, we enrolled individuals from only high-income countries, so our results might not apply to other settings.

Lifelong treatment with potent antiretrovirals means that monitoring the numbers of deaths from specific causes that have been rare until now is crucial. Such monitoring will ensure that any increases are identified at an early stage. The results of our study show that 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-related disorders, cardiovascular disease, liver disease, and non-AIDS cancer is low.

There have been dramatic reductions in rates of AIDS-related, liver-related, and cardiovascular-related deaths, providing support for overall net positive clinical effects of ART in the long term. Non-AIDS cancer deaths are now the most common non-AIDS cause of death. Some potential drug toxicities are cumulative or could be associated with a delay on clinical manifestation so it is important to continue such monitoring in the future.

Contributors

JDL, LRN, CAS, and CJS had the idea for the study and wrote the original protocol. RW, PM, CP, PR, JK, SdW, WeS, OK, NF, and AdAM provided feedback and suggestions on the protocol. CJS wrote the analysis plan and did the analyses with the support of CAS, ANP, and ML. CJS wrote the first draft of the paper, with support from JDL. All authors commented on the first and subsequent drafts of the paper, and provided feedback and suggestions, which were then incorporated into the paper. All authors have seen and approved the final version of the manuscript.

Declaration of interests

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