Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D study

The Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) Study Group

Objective: To investigate any emerging trends in causes of death amongst HIV-positive individuals in the current cART era, and to investigate the factors associated with each specific cause of death.

Design: An observational multicentre cohort study.

Methods: All HIV-positive individuals included in one of the cohorts in the Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) Study were included. The association between HIV-specific and non HIV-specific risk factors and death were studied using multivariable Poisson regression.

Results: We observed 2482 deaths in 180 176 person-years (PY) on 33 308 individuals [rate/1000 PY = 13.8 (95% CI 13.2–14.3)]. Primary causes of death were: AIDS ($n = 743$; rate/1000 PY = 4.12), liver-related (341; 1.89), CVD-related (289; 1.60), non-AIDS malignancy (286; 1.59). The overall rate of death fell from 16.9 in 1999/2000 to 9.6/ 1000 PY in 2007/2008. Smoking was associated with CVD and non-AIDS cancers, HBV and HCV co-infection with liver-related deaths, and hypertension with liver-related and CVD deaths. Diabetes was a risk factor for all specific causes of death except non-AIDS cancers, and higher current HIV RNA for AIDS-related deaths. Lower CD4 cell counts were associated with a higher risk of death from all specific causes of death.

Conclusion: Multiple potentially modifiable traditional and HIV-specific risk factors for death of HIV-infected persons were identified. The maximum reduction in mortality in HIV-infected populations will require that each of these factors be appropriately addressed. No trends in terms of emerging causes of unexpected deaths were observed, although monitoring will continue.

AIDS 2010, **24**:1537–1548

Keywords: death, modifiable risk factors

Background

Although death rates amongst HIV-positive individuals are much lower than those observed in the pre and early-combination antiretroviral therapy (cART) eras [1,2], there remains an excess risk compared with the general population [3,4]. As the cART era has progressed, new information has emerged on rates and causes of death [5,6]. As a result of the dramatic reduction in AIDS-related mortality, the relative importance of other causes of death not previously thought to be HIV-related increases [5], and associations with immunodeficiency have been identified [5,7].

The HIV-positive population in developed countries is one with a high prevalence of risk factors for specific causes of mortality, such as smoking with cardiovascular disease [8] and coinfection with hepatitis C virus (HCV) for liver-related deaths [9]. Thus, identification of risk factors for death in this population may allow the

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Received: 3 December 2009; revised: 10 March 2010; accepted: 18 March 2010.

DOI:10.1097/QAD.0b013e32833a0918

development of strategies for risk factor reduction that could, in turn, have an impact on mortality.

The primary aim of this study was to investigate any emerging trends in causes of death amongst HIV-positive individuals in the current cART era, particularly considering whether there were any unexpected increases in any cause. The second aim was to investigate the factors associated with each specific cause of death.

Methods

Patient population

Individuals included in this study were from the Data Collection on Adverse Events of Anti-HIV Drug (D:A:D) study [10]. In brief, the study is a collaboration of 11 previously established cohorts following HIV-positive individuals at 212 clinics in 21 countries in Europe, the United States, and Australia. Participants are followed prospectively during their regular visits to outpatient clinics. Eligible patients were all under active follow-up in their individual cohorts at the time of D:A:D study recruitment, regardless of their antiretroviral-treatment status. At enrollment, and at least every 8 months thereafter, standardized data-collection forms are completed at the sites. All information collected is then transformed into a standardized format and merged into a central dataset. The present analysis is performed on data merged in September 2008, with data complete to February 2008.

Classification of causes of death

Information on death is collected prospectively, and with primary and secondary causes of death classified using the CoDE system. This is a uniform coding system that can be applied to studies of HIV-positive individuals, including detailed data collection on the causes of death and contributing factors, as well as a centralized review process of the data collected [10]. A physician or appointed healthcare staff member from the treating centre initially completes a CoDe case report form (CRF). A cause of death is then assigned using a predefined algorithm by at least two independent expert reviewers, with a further process in place to resolve any differences of opinion. Codes are adapted from ICD-10 codes to ensure that causes of death in HIV-positive individuals are sufficiently captured [11]. The underlying cause attributed to each death is considered in our primary analyses. For certain analyses these were grouped into the following five broader categories: CVD-related, HIV/AIDS-related, liver-related, non-AIDS malignancy and other/unknown.

Statistical methods

All D:A:D study participants were included in analyses. Follow-up for each individual began on the date of their study entry, and ceased at the date of death, the date of loss to follow-up, or the end of study follow-up (February 2008), whichever occurred first. As in previous analyses performed using the D:A:D dataset, each individual's follow-up was divided into 1 month periods, and the characteristics of the individual at the beginning of the month were determined. Thus, time-varying factors were allowed to change over time, using a time-updated analytical approach.

Rates of death were calculated for each specific underlying cause of death, and for each of the broader categories. These rates were then stratified by calendar year and latest (time-updated, lagged by 6 months) CD4 cell count. Finally, Poisson regression models were used to identify factors associated with each specific cause of death. Each of the five broader categories was considered in a separate model; those dying of a cause other than the one currently under consideration were censored on their date of death. Potential risk factors considered were: CD4 cell count, HIV RNA viral load/ART status, BMI, smoking status, diabetes mellitus, calendar year, age, race, risk for HIV transmission, sex, hypertension and hepatitis B and C status (HBV and HCV). Hypertension was defined as systolic blood pressure more than 140 mmHg, diastolic blood pressure more than 90 mmHg and/or receipt of at least one antihypertensive; HCV infection was defined as positive surface antibody or detectable HCV RNA; HBV infection was defined as positive antigen or antibody, or HBV DNA positive. Thus, chronic, active and previous infections were included. With the exception of age, risk and sex, all variables were time-updated. In addition, CD4 cell count, HIV-RNA status, BMI and hypertension were lagged by 6 months, which means that the value attributed to the variable at any point in follow-up is the most recently measured value at a time point 6 months previously. This was to ensure that the level of the variable was less likely to reflect the consequences of (as opposed to being a potential cause of) an illness that then led to death. As HIV RNA status is highly dependent on receipt of ART, this variable was combined with current ART use (on ART with HIV RNA < 2.6 log copies/ml; HIV RNA > 2.6 log copies/ml, on ART; HIV RNA < 4 log copies/ml, off ART; HIV RNA 4–5 log copies/ml, off ART and HIV RNA >5 log copies/ml, off ART). Multivariable analyses included all potential risk factors in the same model, regardless of their significance in univariable analyses. Although only multivariable results are presented, univariable analyses showed similar risk ratios to those presented here. We also found similar results when firstly repeating our analyses for causes of death, regardless of whether it was the underlying or a secondary cause and secondly excluding those who died from any cause other than the one currently being studied to ensure that results could not be explained by competing risks. Again, results were similar to those presented here. Analyses were performed using SAS Version 9 (Cary, North Carolina,

USA) and a *P*-value of less than 0.05 was considered statistically significant. No statistical adjustments were made for the number of models that were performed, and missing categories were created for missing data.

Results

Patient characteristics

The characteristics of the 33 308 participants at study entry are shown in Table 1. The median (inter-quartile range) time since entering their respective cohort was 3.0 (0.7, 5.6) years, with 3811 (11.4%) entering both their own cohort and the D:A:D study at the same time. Of note, 15.3% (5082) and 11.5% (3815) were HCV and HBV infected, respectively, 34.7% (11 572) and 18.4% (6120) were current or ex-smokers, respectively, 2.9% (976) had diabetes mellitus and 14.0% (4663) had hypertension. The median (inter-quartile range) CD4 cell count was 408 (249, 600) cells/μl and 48.6% (15595/32085) had HIV RNA less than 400 copies/ml. At study entry, 24374 (73.2%) individuals had ever received ART (median duration 3.1 years).

Rate of death

There were 2482 deaths in 180 176 person-years of follow-up, leading to a rate of all-cause mortality of 13.8 (95% CI 13.2, 14.3) per 1,000 person-years (Table 2). The most common causes of death were HIV/AIDS (743; 29.9% of deaths), liver-related death (341, 13.7%), CVD-related death (289, 11.6%) and non-AIDS malignancies (286; 11.5%). Other known causes accounting for more than 2% of all deaths were invasive bacterial infection (166; 6.7%), suicide (96; 3.9%) and drug overdose (63; 2.5%).

Association between calendar time and rate of death

For many causes the rate of death decreased over time (Fig. 1 and Table 2): deaths due to AIDS decreased from 5.62 per 1000 person years in 1999/2000 to 1.75 per 1000 person years in 2007/2008. Rates of death also fell for chronic viral hepatitis, liver failure, myocardial infarction,

Table 1. Characteristics of D:A:D study participants at study entry.

		Number (percentage)
Total number		33308 (100.0)
Time under cohort follow-up when enrolled into D:A:D (years)	Median (IQR)	3.0 (0.7, 5.6)
Sex	Male	24669 (74.1)
HIV risk group	Homosexual	14388 (43.2)
	Heterosexual	10017 (30.1)
	IDU	5997 (18.0)
	Other/Unknown	2906 (8.7)
Ethnicity	White	17835 (53.6)
	Black	3548 (10.7)
	Other	1051 (3.2)
	Unknown	10874 (32.7)
Age (years)	Median (IQR)	39 (34, 45)
HCV status %	Positive	5082 (15.3)
	Negative	16741 (50.3)
	Unknown	11485 (34.5)
HBV status[%]	Positive	3815 (11.5)
	Negative	18161 (54.5)
	Unknown	11332 (34.0)
BMI (kg/m^2)	Median (IQR)	$N=28852$ 23 (21, 25)
Smoking status	Current	11572 (34.7)
	Ex	6120 (18.4)
	Never	9014 (27.1)
	Unknown	6602 (19.8)
Diabetes mellitus	Yes	976 (2.9)
Hypertensive[#]	Yes	4663 (14.0)
HIV RNA ($\log_{10}$ copies/ml)	Median (IQR)	$N=32085$ 2.7 (1.7, 4.2)
CD4 cell count (cells/μl)	Median (IQR)	$N=32442$ 408 (249, 600)
CD4 cell count <200 cells/μl	Yes	7022 (21.1)
CD4 cell count <350 cells/μl	Yes	14133 (42.4)
Prior AIDS diagnosis	Yes	7668 (23.0)
Cumulative ART exposure (years)*	Median (IQR)	$N=24374$ 3.1 (1.6, 4.8)
Cumulative cART exposure (years)*	Median (IQR)	$N=22541$ 2.4 (1.2, 3.4)
Cumulative PI exposure (years)*	Median (IQR)	$N=19310$ 2.3 (1.2, 3.2)
Cumulative NNRTI exposure (years)*	Median (IQR)	$N=11067$ 0.9 (0.4, 1.6)

ART, antiretroviral therapy; BMI, body mass index; cART, combination ART; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, intravenous drug use; IQR, inter quartile range; NNRTI, non-NRTI; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; [%]HCV positive defined as positive surface antibody or detectable HCV RNA; HBV positive defined as positive antigen or antibody, or HBV DNA positive.
*Amongst those with >0 year exposure.
[#]Systolic BP >140 mmHg or diastolic BP >90 mmHg or receiving at least one antihypertensive.

Table 2. Primary (underlying) causes of death in D:A:D study.

	Number (% of total deaths)	Rate of death* (95% CI)	Rate of death in 1999/2000 (95% CI)	Rate of death in 2007/2008 (95% CI)
Total deaths	2482 (100.0)	13.8 (13.2, 14.3)	16.9 (14.9, 19.1)	9.60 (8.24, 11.0)
AIDS	743 (29.9)	4.12 (3.83, 4.42)	5.62 (4.40, 6.84)	1.75 (1.17, 2.33)
Liver-related	341 (13.7)	1.89 (1.69, 2.09)	2.67 (1.83, 3.51)	1.45 (0.92, 1.98)
Chronic viral hepatitis	285 (11.5)	1.58 (1.40, 1.77)	2.12 (1.38, 2.87)	1.25 (0.76, 1.74)
Liver failure[a]	56 (2.3)	0.31 (0.23, 0.39)	0.55 (0.24, 1.08)	0.20 (0.05, 0.51)
CVD-related	289 (11.6)	1.60 (1.42, 1.79)	1.71 (1.04, 2.38)	1.50 (0.96, 2.04)
MI, definite or possible	157 (6.3)	0.87 (0.74, 1.01)	1.16 (0.68, 1.87)	0.55 (0.27, 0.98)
Stroke	35 (1.4)	0.19 (0.13, 0.26)	0.14 (0.02, 0.50)	0.30 (0.11, 0.65)
Other CVD	36 (1.5)	0.20 (0.13, 0.27)	0.00 (0.00, 0.25)	0.35 (0.14, 0.72)
Other heart disease	54 (2.2)	0.30 (0.22, 0.38)	0.34 (0.11, 0.80)	0.30 (0.11, 0.65)
Complications due to diabetes mellitus	7 (0.3)	0.04 (0.02, 0.08)	0.07 (0.00, 0.38)	0.00 (0.00, 0.18)
Non-AIDS malignancy[b]	286 (11.5)	1.59 (1.40, 1.77)	1.44 (0.82, 2.05)	1.10 (0.64, 1.56)
Other/Unknown	823 (33.2)	4.57 (4.26, 4.88)	5.55 (4.34, 6.76)	3.80 (2.94, 4.65)
Suicide	96 (3.9)	0.53 (0.43, 0.64)	0.82 (0.42, 1.44)	0.35 (0.14, 0.72)
Drug overdose	63 (2.5)	0.35 (0.26, 0.44)	0.82 (0.42, 1.44)	0.00 (0.00, 0.18)
Euthanasia	5 (0.2)	0.03 (0.01, 0.07)	0.00 (0.00, 0.25)	0.10 (0.01, 0.36)
Homicide	14 (0.6)	0.08 (0.04, 0.13)	0.27 (0.07, 0.70)	0.00 (0.00, 0.18)
Accident	38 (1.5)	0.21 (0.14, 0.28)	0.07 (0.00, 0.38)	0.05 (0.00, 0.28)
Invasive bacterial infection	166 (6.7)	0.92 (0.78, 1.06)	0.89 (0.47, 1.52)	0.40 (0.17, 0.79)
Lactic acidosis	15 (0.6)	0.08 (0.05, 0.14)	0.00 (0.00, 0.25)	0.00 (0.00, 0.18)
Pancreatitis	17 (0.7)	0.09 (0.05, 0.15)	0.21 (0.04, 0.60)	0.00 (0.00, 0.18)
Renal dysfunction or disease	29 (1.2)	0.16 (0.10, 0.22)	0.14 (0.02, 0.50)	0.05 (0.00, 0.28)
Other	248 (10.0)	1.38 (1.20, 1.55)	1.98 (1.26, 2.71)	1.80 (1.21, 2.38)
Unknown	132 (5.3)	0.73 (0.61, 0.86)	0.34 (0.11, 0.80)	1.05 (0.60, 1.50)

There were a total of 180 176 person-years of follow-up available.
*Rates and 95% confidence intervals are given per 1000 person-years of follow-up.
[a]Defined as conditions not related to chronic infection with hepatitis B or C, but where 'liver failure' is present.
[b]Includes lung cancers, prostate cancers, anal cancers, Hodgkin's lymphomas, primary liver cancers, gastrointestinal cancers, breast cancers, uterus cancers, testicular cancers, bladder cancers and leukemias.

suicide and drug overdose. There were no other obvious trends observed, with the exception of deaths in the 'unknown' category, which increased from 0.34 per 1000 person years in 1999/2000 to 1.05 in 2007/2008.

CD4 cell count association with specific causes of death

Analyses from this point forward considered the broader categories for causes of death. There was an association between the CD4 cell count and each cause of death considered (Fig. 2), but there were differences in the strength of these associations. For example, liver-related deaths were strongly associated with immunodeficiency in these unadjusted analyses, as the rate was 8.30 per 1000 person-years for those with latest CD4 cell counts less than 50 cells/μl and 0.58 per 1000 person-years for more than 500 cells/μl. In contrast, the association with CVD-related death was much weaker, with rates of death of 3.11 and 1.16 per 1000 person-years respectively for these CD4 cell categories.

Non-HIV specific potentially modifiable factors

Results from Poisson regression models investigating the factors associated with each cause of death are shown in Table 3. Smoking status was associated with an increased risk of death from all-cause, non-AIDS malignancies, and CVD-related and other causes. Compared with those with a BMI of 18–25 kg/m^2, those with a BMI at least 18 kg/m^2 were at increased risk of deaths from all-cause, AIDS-related, non-AIDS malignancies, CVD-related and other causes. At the other end of the spectrum, those with a BMI more than 30 kg/m^2 had a decreased risk of AIDS-related death and an increased risk of death from CVD-related causes, although the confidence interval for the latter association was wide. Both those with hypertension and those with diabetes mellitus were at an increased risk of death from all-cause, AIDS-related, liver-related, CVD-related and other causes. Finally, HCV and HBV were only associated with all-cause, liver-related deaths and deaths from other causes.

HIV-specific potentially modifiable risk factors

Higher CD4 cell counts were strongly associated with a lower risk of mortality from all causes considered, with the possible exception of CVD-related deaths, where this association was marginally significant at the 5% level. Compared with ART-treated individuals with HIV RNA less than 2.6 $\log_{10}$ copies/ml, treated individuals with HIV RNA levels above this cut-off had a higher risk of all-cause, AIDS-related death and other causes. For the remaining causes of death, there was also evidence of a trend towards a greater risk of death amongst those with higher HIV RNA levels. Among untreated individuals, there was a particularly strong association between higher HIV RNA levels (compared with treated patients with HIV RNA levels <2.6 $\log_{10}$ copies/ml) and an increased risk of death from AIDS-related causes.

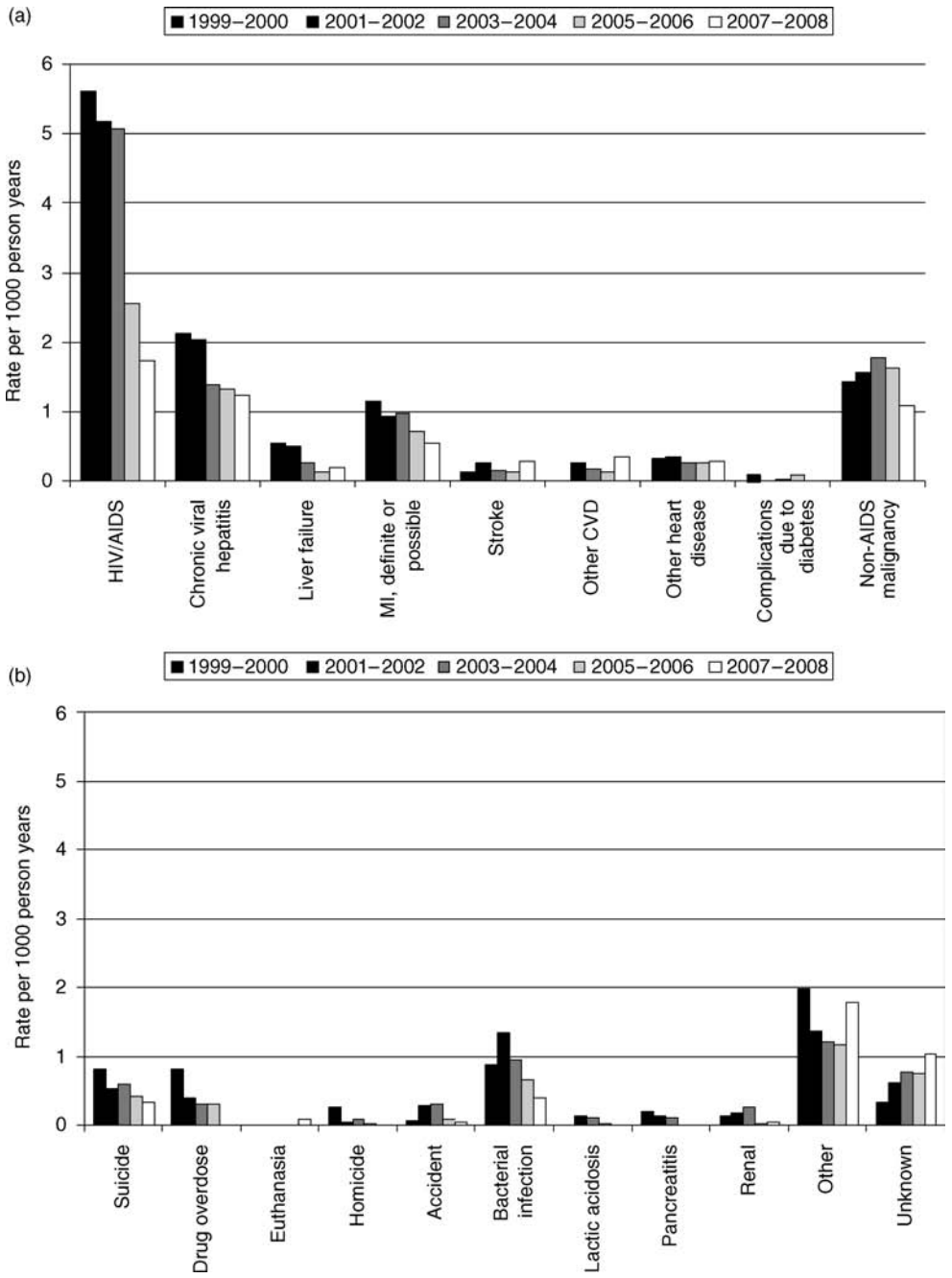

Fig. 1. Rate of death according to calendar year and specific cause of death. (a) AIDS-related, Liver-related, CVD-related, and non-AIDS malignancy deaths. (b) Other causes of death. Footnote: rates calculated by dividing number of deaths by total length of follow-up and presented per 1000 person years. Person years available in 1999/2000 = 14593; 2001/2002 = 45599; 2003/2004 = 52700; 2005/2006 = 47279; 2007/2008 = 20004.

Nonmodifiable risk factors

Males had a 1.32 times the risk of death from 'other' causes compared with females, and there was also a trend towards an association with CVD-related deaths. Older age was associated with an increased risk of death from all causes considered, with the strongest associations for deaths due to non-AIDS malignancies and CVD-related causes. Compared with those of white ethnicity, those of black ethnicity were at a decreased risk of death from AIDS-related causes and an increased risk of death from other causes. As expected, those with an intravenous drug use risk for HIV transmission were at an increased risk of death from all-cause, liver-related, CVD-related and other causes compared with those with a homosexual

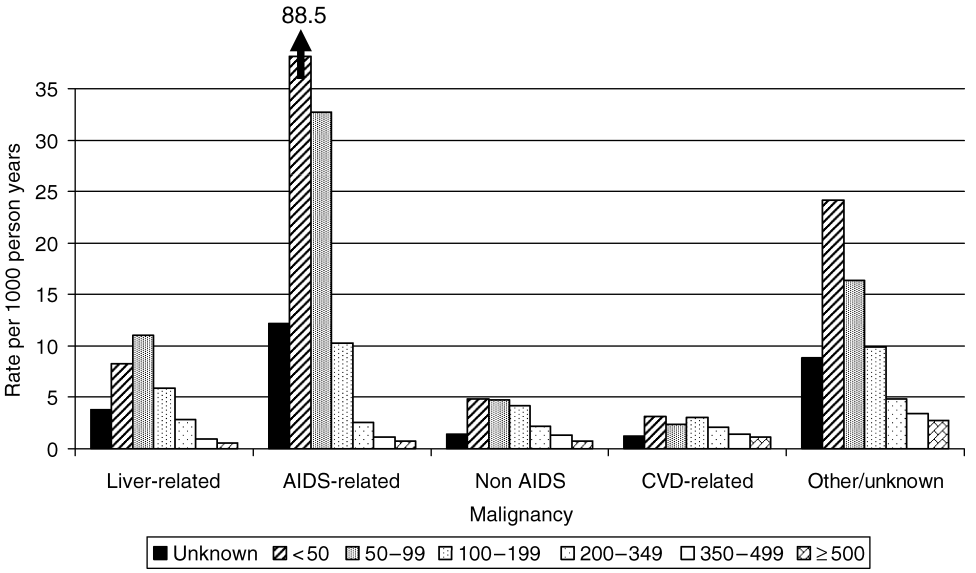

Fig. 2. Death rates per 1000 person years of follow-up, stratified by latest CD4 cell count (cells/μl; lagged by 6 months). Footnote: rates calculated by dividing number of deaths by total length of follow-up and presented per 1000 person years. Person years available for unknown CD4 cell count = 4194; <50 cells/μl = 2891; 50–99 cells/μl = 3359; 100–199 cells/μl = 12782; 200–349 cells/μl = 35490; 350–499 cells/μl = 42231; ≥500 cells/μl = 79227.

risk. Finally, later calendar years were associated with a reduced risk of death from all causes considered.

Discussion

Our study suggests that the decreases in mortality observed in HIV-positive populations in the pre and early-cART eras are continuing. It is particularly encouraging that there was no evidence that rates of death from any specific cause were increasing over the study period, and no emerging trends in unexpected causes of deaths were identified. This was reflected in the fact that the most common cause of death was the 'Other/Unknown' category. Unfortunately, none of the causes included in this category contained sufficient numbers for us to consider them separately when investigating potential risk factors. Nonetheless, it is reassuring that the numbers of each cause of death were low. There was evidence of an increase in rates of death due to unknown and other causes, although the number of deaths in this category remains relatively small. This may simply reflect a delay in ascertainment, rather than an increase in unusual causes of death. Monitoring for unexpected trends in specific causes of death will continue in DAD.

One of the most striking findings of this study is that, although the overall rate has decreased and is much lower than that observed in the pre-cART era, AIDS-related illness remained the most common cause of death. This is despite the fact that this study was conducted in the years 1999–2008 in countries with good and often free access to antiretroviral treatment. It can be seen from Fig. 2 that the AIDS-related deaths were particularly prevalent amongst those with the lowest CD4 cell counts, and substantially reduced amongst those with higher CD4 cell counts. However, most patients (89%) were already under care at their respective clinics for a median of 3 years and so most patients had the opportunity to be stabilized under care (including the opportunity for increases in CD4 cell count to be achieved), and were presumably at a decreased risk of mortality compared with recent late presenters. The high proportion of AIDS-related deaths is particularly concerning with this in mind. Our finding that the next most common causes of death were liver-related, CVD-related and non-AIDS malignancies, is consistent with findings from other studies [5,12,13]. It is encouraging that rates of other causes of death, such as renal dysfunction [14], lactic acidosis [15] and pancreatitis [16] remain low, as suggested in other studies. The previously observed relatively high rates of death from nonnatural causes, such as, overdose and suicide, is particularly worrying [5]. There may be a high prevalence of drug and alcohol use, or high levels of psychiatric disease, or a higher occurrence of high-risk behaviour as observed in previous studies [17,18].

In recent years, HIV-specific risk factors, such as the CD4 cell count, have been shown to be associated with a wider range of morbidities than previously thought [5,7,19,20] and this finding was confirmed in this present study. Additionally, it suggests that reduction of viral load through use of ART is associated with a reduction in mortality from the causes studied, agreeing with the

Table 3. Factors associated with specific causes of death: results of multivariable Poisson regression model.

	Adjusted relative rate (95% CI) of death					
	All cause	AIDS-related	Liver-related	Non-AIDS malignancies	CVD-related	Other/unknown
Sex (ref female)						
Male	1.22 (1.08, 1.37)	1.08 (0.86, 1.35)	1.21 (0.90, 1.62)	1.01 (0.70, 1.46)	1.36 (0.93, 2.00)	1.32 (1.08, 1.61)
Current age						
Per 5 years older	1.25 (1.22, 1.28)	1.12 (1.07, 1.16)	1.16 (1.09, 1.24)	1.47 (1.40, 1.55)	1.46 (1.38, 1.54)	1.26 (1.21, 1.31)
Race (ref White)						
Black	1.13 (0.96, 1.34)	0.74 (0.56, 0.98)	0.74 (0.40, 1.39)	1.17 (0.66, 2.08)	1.33 (0.77, 2.29)	1.53 (1.15, 2.03)
Other	0.89 (0.66, 1.20)	0.73 (0.45, 1.18)	0.88 (0.36, 2.19)	1.33 (0.58, 3.08)	0.63 (0.20, 1.99)	0.90 (0.53, 1.53)
Unknown	1.01 (0.91, 1.11)	0.96 (0.80, 1.14)	1.09 (0.84, 1.40)	1.37 (1.05, 1.78)	0.95 (0.72, 1.24)	0.94 (0.80, 1.12)
Risk for HIV (ref homosexual)						
IDU	1.80 (1.58, 2.05)	0.92 (0.71, 1.19)	5.02 (3.56, 7.08)	1.18 (0.78, 1.80)	1.83 (1.23, 2.72)	2.24 (1.80, 2.78)
Heterosexual	0.83 (0.73, 0.94)	0.79 (0.63, 1.00)	1.06 (0.70, 1.59)	0.76 (0.53, 1.07)	0.68 (0.47, 0.98)	0.89 (0.71, 1.11)
Other/unknown	1.11 (0.95, 1.29)	0.89 (0.68, 1.16)	1.67 (1.03, 2.71)	0.79 (0.50, 1.25)	0.88 (0.56, 1.39)	1.36 (1.04, 1.77)
Calendar year (ref 2003–2004)						
1999–2000	1.18 (0.98, 1.41)	0.92 (0.67, 1.26)	1.48 (0.92, 2.39)	0.91 (0.49, 1.66)	1.26 (0.71, 2.23)	1.34 (0.99, 1.82)
2001–2002	1.09 (0.98, 1.21)	0.91 (0.75, 1.09)	1.41 (1.06, 1.88)	0.96 (0.70, 1.31)	1.24 (0.91, 1.70)	1.10 (0.92, 1.33)
2005–2006	0.76 (0.68, 0.85)	0.67 (0.53, 0.83)	0.91 (0.66, 1.25)	0.82 (0.60, 1.11)	0.77 (0.56, 1.07)	0.79 (0.65, 0.97)
2007–2008	0.73 (0.62, 0.85)	0.56 (0.39, 0.80)	0.93 (0.61, 1.43)	0.51 (0.32, 0.82)	0.77 (0.50, 1.17)	0.87 (0.67, 1.14)
Current smoking status (ref never)						
Smoker	1.44 (1.27, 1.64)	0.94 (0.75, 1.20)	1.15 (0.81, 1.64)	2.20 (1.48, 3.26)	1.90 (1.29, 2.80)	1.62 (1.29, 2.04)
Ex smoker	1.40 (1.23, 1.60)	1.05 (0.83, 1.34)	0.97 (0.67, 1.41)	2.52 (1.73, 3.67)	1.98 (1.36, 2.88)	1.37 (1.08, 1.73)
Unknown	1.59 (1.37, 1.85)	1.38 (1.08, 1.77)	0.71 (0.43, 1.18)	1.93 (1.20, 3.09)	2.12 (1.35, 3.34)	1.69 (1.29, 2.21)
Current BMI (ref 18–25 kg/m^2; lagged 6 months)						
<18 kg/m^2	2.46 (2.13, 2.84)	2.70 (2.13, 3.42)	1.13 (0.69, 1.85)	2.03 (1.28, 3.21)	1.98 (1.18, 3.33)	2.83 (2.21, 3.62)
26–30 kg/m^2	0.64 (0.55, 0.75)	0.62 (0.46, 0.84)	0.90 (0.63, 1.30)	0.63 (0.41, 0.96)	0.51 (0.33, 0.80)	0.65 (0.50, 0.84)
>30 kg/m^2	0.96 (0.78, 1.17)	0.57 (0.35, 0.93)	0.97 (0.56, 1.69)	0.94 (0.52, 1.71)	1.44 (0.90, 2.29)	1.09 (0.79, 1.51)
Unknown	1.46 (1.27, 1.67)	1.16 (0.90, 1.49)	1.75 (1.23, 2.48)	1.23 (0.81, 1.87)	1.91 (1.32, 2.76)	1.49 (1.18, 1.89)
Current hypertension (lagged 6 months)						
Yes vs. no	1.52 (1.38, 1.68)	1.30 (1.07, 1.58)	2.34 (1.83, 2.99)	1.01 (0.77, 1.34)	2.04 (1.57, 2.66)	1.48 (1.25, 1.76)
Current diabetes mellitus						
Yes vs. no	1.77 (1.54, 2.03)	1.48 (1.11, 1.97)	2.37 (1.68, 3.35)	1.22 (0.80, 1.85)	1.83 (1.29, 2.59)	1.88 (1.49, 2.38)
HCV status (ref uninfected)						
HCV infected	1.21 (1.06, 1.38)	1.04 (0.80, 1.35)	1.67 (1.21, 2.31)	0.98 (0.63, 1.53)	1.37 (0.91, 2.06)	1.30 (1.04, 1.63)
HCV unknown	1.07 (0.97, 1.18)	0.96 (0.80, 1.15)	1.67 (1.27, 2.21)	1.00 (0.76, 1.32)	1.07 (0.81, 1.42)	1.07 (0.90, 1.27)
HBV status (ref uninfected)						
HBV infected	1.21 (1.07, 1.37)	0.93 (0.73, 1.18)	2.37 (1.74, 3.22)	0.98 (0.67, 1.44)	1.11 (0.77, 1.61)	1.26 (1.01, 1.57)
HBV unknown	0.99 (0.90, 1.09)	0.83 (0.69, 1.00)	1.66 (1.28, 2.17)	0.93 (0.71, 1.23)	0.83 (0.63, 1.10)	1.12 (0.96, 1.32)
Latest CD4 cell count (lagged 6 months)						
Per 50 cells/μl increase	0.86 (0.85, 0.87)	0.66 (0.64, 0.68)	0.82 (0.79, 0.85)	0.90 (0.88, 0.93)	0.97 (0.95, 0.99)	0.92 (0.91, 0.94)
Latest HIV RNA and ART status (lagged 6 months) ref <2.6 log copies/ml on ART						
HIV RNA >2.6 log copies/ml, on ART	1.55 (1.41, 1.71)	2.21 (1.80, 2.72)	1.20 (0.92, 1.56)	1.27 (0.96, 1.67)	1.19 (0.89, 1.59)	1.43 (1.20, 1.71)
HIV RNA <4 log copies/ml, off ART	1.43 (1.20, 1.70)	1.80 (1.20, 2.71)	1.25 (0.82, 1.92)	0.81 (0.45, 1.47)	0.76 (0.43, 1.35)	1.80 (1.40, 2.31)
HIV RNA 4–5 log copies/ml, off ART	1.42 (1.20, 1.67)	3.15 (2.37, 4.19)	1.15 (0.73, 1.81)	0.63 (0.33, 1.20)	0.80 (0.44, 1.44)	1.24 (0.92, 1.67)
HIV RNA >5 log copies/ml, off ART	3.13 (2.66, 3.68)	5.35 (4.11, 6.98)	1.68 (1.01, 2.80)	1.26 (0.64, 2.48)	1.16 (0.54, 2.48)	2.93 (2.18, 3.95)

Results from multivariable Poisson regression models (one separate model for each cause of death). 95% CI, 95% confidence interval; ART, antiretroviral therapy; BMI, body mass index; CVD, cardiovascular disease; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injecting drug user; ref, reference. Hypertensive defined as systolic BP >140 mmHg or diastolic BP >90 mmHg or receiving at least one antihypertensive; HCV positive defined as positive surface antibody or detectable HCV RNA; HBV positive defined as positive antigen or antibody, or HBV DNA positive. CD4 cell count, HIV-RNA status, BMI and hypertension were lagged by 6 months. Thus, the 'latest' measurement for these variables had to have been measured at least 6 months prior to death (or the latest time point for those remaining alive).

findings of the recent SMART randomized trial [21]. However, although we believe that modification of non-HIV specific risk factors would result in significant clinical benefit, there is little evidence as yet suggesting this is true for HIV-specific factors, particularly for those with high CD4 cell counts (>350 cells/μl). Further study of this issue, through randomized comparisons such as the upcoming Strategic Timing of Antiretroviral Treatment (START) trial, is warranted [22–24]. In addition to any effect of receipt of ART on mortality, the effect of

duration of ART amongst fully suppressed individuals is not known.

With HIV-infected individuals increasingly responding well to antiretroviral treatment, it is likely that the proportion of deaths due to non-AIDS causes will increase. Smoking was associated with increased risk of death, particularly CVD and non-AIDS malignancies, as has been seen in HIV-negative populations [3]. Of particular interest is the fact that the relative risks for ex-smokers were similar to those for current smokers. Studies in the general population suggest that although smoking cessation leads to decreased risk, ex-smokers remain at an excess risk for a number of years after cessation, with the risk of malignancy in particular remaining raised for up to 10 years [25]. Precise information on the time as smoking cessation was not available, and so it is possible that some of the ex-smokers had only recently given up, perhaps even as a result of feeling unwell, explaining the similar risks observed. To date, the impact of interventions for smoking cessation in HIV-populations have been extremely limited [26,27], similarly to those in the general population [28]. Despite this, renewed efforts to promote smoking cessation could lead to long-term reductions in mortality.

Diabetes mellitus and hypertension were associated with an increased risk of all causes of mortality considered, with the exception of non-AIDS malignancies. Diabetes mellitus may be a risk factor as a result of bacterial infections through higher glucose levels in the blood, ascites and urine. However, reasons for the associations with hypertension are not obvious. As expected, those who were HCV or HBV positive were at a greater risk of liver-related death [29,30]. Although the excess mortality risk may also be partly explained by other lifestyle factors [31], much of this mortality risk is likely due to exposure to the viruses themselves. The impact of HBV infection is likely to be modified in the long-term by the antiviral activity of some current antiretrovirals against the hepatitis B virus [32], as lower HBV DNA levels have been associated with reduced risk of death [33]. In contrast, although anti-HCV treatment has improved in recent years and is associated with increased survival [34], cure rates of HCV remain low, especially for those of genotype 1, and the number of HIV-positive patients meeting the strict criteria for HCV treatment has remained low [35]. In the future, the introduction of novel treatments such as specifically targeted antiviral therapy (STAT-C) may increase these cure rates further. It is reassuring that no association was seen with other mortality causes, with the exception of other causes.

Those with lower BMIs were at an increased risk of AIDS-related, non-AIDS malignancies, CVD-related and other deaths. These conditions are frequently chronic in nature and the association with lower BMI may merely be a marker of a subgroup already with these types of diseases. Extending the lag time to the BMI value considered did not however materially attenuate the association. At the other end of the spectrum, it was surprising there was not a stronger association between BMI more than 30 kg/m^2 and risk of death from CVD-related causes, although the confidence interval was particularly wide, reflecting the fact that there is a low prevalence of high BMI in HIV-positive individuals.

We also gained information on the effect of nonmodifiable risk factors on mortality. Older age was associated with an increased risk of all causes of mortality considered, as expected. After adjustment for factors including current CD4 cell count, those of black and other ethnicity were at a decreased risk of death from AIDS-related death and an increased risk of death from other causes compared with whites. Differences may be due to other socioeconomic and lifestyle factors, and loss to follow-up did differ slightly between groups (the rate of loss to follow-up was 3.4 per 100 person-years among whites, 3.9 among blacks and 2.7 among others) [36]. Surprisingly, male sex was only associated with a greater risk of death from other causes, and marginally associated with a greater risk of CVD-related deaths, although previous studies on this cohort looking at both fatal and nonfatal myocardial infarctions have revealed a much more marked association [37]. Those with an IDU risk for HIV transmission were at an increased risk of liver-related death, most probably as a result of residual confounding with HCV and HBV status or the effect of alcohol-associated diseases. They were also at an increased risk of CVD/other heart disease-related death, likely due to endocarditis secondary to injecting drugs, as well as use of cocaine and amphetamine that can cause vasoconstriction and myocardial infarction if used excessively.

The D:A:D study is an ideal cohort for studying emerging trends in causes of death, due to its large sample size. It is to be hoped that use of this dataset could help identify any trends in causes of death at an early time point, which could then be investigated further as necessary. Furthermore, the study, through the use of the CoDe system, has established a method by which causes of death are prospectively collected and recorded. Unfortunately, questions on factors associated with causes of death could not easily be studied in a randomized setting (e.g. due to issues with sample size and representativeness) and thus observational studies such as these are invaluable. However, the observational nature means we cannot rule out the presence of unmeasured confounding. Although we collect detailed information on a number of non-HIV specific risk factors, information on some possible risk factors, such as alcohol use, was not available. Also, these results clearly apply to the developed world setting, where the prevalence of mortality risk factors is likely to be different to other settings. Finally, we only considered morbidity that led to death; investigation of work into

both fatal and nonfatal outcomes will be considered in future years.

Conclusion

In summary, this study has found no emerging trends in unexpected causes of deaths amongst HIV infected individuals in the years 1999–2008. It also reiterates the importance of addressing traditional, non-HIV specific risk factors. Further reductions in mortality in HIV-infected populations may only be possible if these modifiable factors are appropriately addressed. Additionally, although high CD4 cell counts and control of HIV replication are associated with reduced risk of death for some specific non-AIDS-related causes, there is as yet limited evidence that modifying these markers will reduce the risk of non-AIDS mortality. Further research into this issue is required.

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Supported by the Oversight Committee for The Evaluation of Metabolic Complications of HAART, a collaborative committee with representation from academic institutions, the European Agency for the evaluation of Medicinal Products, the Food and Drug Administration, the patient community, and all pharmaceutical companies with licensed anti-HIV drugs in the United States market. Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, and Hoffman-LaRoche. Supported by a grant (CURE/97–46486) from the Health Insurance Fund Council, Amstelveen, the Netherlands, to the AIDS Therapy Evaluation Project Netherlands (ATHENA); by a grant from the Agence Nationale de Recherches sur le SIDA (Action Coordonnée no.7, Cohortes), to the Aquitaine Cohort; AHOD is funded by the Australian Government Department of Health and Ageing and is supported in part by grants from the United States National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) grant no U01-AI069907, and the Foundation for AIDS Research; by grants from the Fondo de Investigación Sanitaria (FIS 99/0887) and Fundación para la Investigación y la Prevención del SIDA en Espanã (FIPSE 3171/00), to the Barcelona Antiretroviral Surveillance Study (BASS); by the National Institute of Allergy and Infectious Diseases, National Institutes of Health (grants 5U01AI042170-10 and 5U01AI046362-03), to the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA); by grants from the BIOMED 1 (CT94-1637) and BIOMED 2 (CT97-2713) programs and the fifth framework program (QLK2-2000-00773) of the European Commission and grants from Bristol-Myers Squibb, GlaxoSmithKline, Boehringer Ingelheim, and Roche, to the EuroSIDA study; by unrestricted educational grants of Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GSK, Pfizer, Janssen-Cilag to the Italian Cohort Naive to Antiretrovirals (The ICONA Foundation); and by a grant from the Swiss National Science Foundation, to the Swiss HIV Cohort Study (SHCS).

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