Long-term exposure to combination antiretroviral therapy and risk of death from specific causes: no evidence for any previously unidentified increased risk due to antiretroviral therapy

Justyna D. Kowalska[a], Joanne Reekie[b], Amanda Mocroft[b], Peter Reiss[c], Bruno Ledergerber[d], Jose Gatell[e], Antonella d'Arminio Monforte[f], Andrew Phillips[b], Jens D. Lundgren[a,g], and Ole Kirk[a,g] for the EuroSIDA study group

Background: Despite the known substantial benefits of combination antiretroviral therapy (cART), cumulative adverse effects could still limit the overall long-term treatment benefit. Therefore we investigated changes in the rate of death with increasing exposure to cART.

Methods: A total of 12 069 patients were followed from baseline, which was defined as the time of starting cART or enrolment into EuroSIDA whichever occurred later, until death or 6 months after last follow-up visit. Incidence rates of death were calculated per 1000 person-years of follow-up (PYFU) and stratified by time of exposure to cART (≥3 antiretrovirals): less than 2, 2–3.99, 4–5.99, 6–7.99 and more than 8 years. Duration of cART exposure was the cumulative time actually receiving cART. Poisson regression models were fitted for each cause of death separately.

Results: A total of 1297 patients died during 70 613 PYFU [incidence rate 18.3 per 1000 PYFU, 95% confidence interval (CI) 17.4–19.4], 413 due to AIDS (5.85, 95% CI 5.28–6.41) and 884 due to non-AIDS-related cause (12.5, 95% CI 11.7–13.3). After adjustment for confounding variables, including baseline CD4 cell count and HIV RNA, there was a significant decrease in the rate of all-cause and AIDS-related death between 2 and 3.99 years and longer exposure time. In the first 2 years on cART the risk of non-AIDS death was significantly lower, but no significant difference in the rate of non-AIDS-related deaths between 2 and 3.99 years and longer exposure to cART was observed.

Conclusion: In conclusion, we found no evidence of an increased risk of both all-cause and non-AIDS-related deaths with long-term cumulative cART exposure.

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[a]Copenhagen HIV Programme, University of Copenhagen, Denmark, [b]University College London Medical School, Royal Free Campus, London, UK, [c]Academic Medical Center, Amsterdam, The Netherlands, [d]Division of Infectious Diseases and Hospital Epidemiology, University Hospital, University of Zürich, Zürich, Switzerland, [e]Hospital Clinic, University of Barcelona, Barcelona, Spain, [f]Hospital San Paolo, University of Milan, Milan, Italy, and [g]Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark.

Correspondence to Justyna D. Kowalska, Copenhagen HIV Programme, University of Copenhagen, Faculty of Health Sciences, The Panum Institute/Building, 21.1 Blegdamsvej 3B, DK-2200 Copenhagen N, Denmark.

Tel: +45 35 45 57 67; fax: +45 35 45 57 58; e-mail:jko@cphiv.dk
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Introduction

It is well documented that the survival of HIV-positive patients has significantly improved following the widespread introduction of combination antiretroviral therapy (cART) [1,2]. Within the same time span significant changes in cause-specific mortality have been observed in terms of substantial increase in the proportion of non-AIDS-related deaths such as non-AIDS-defining malignancies, cardiovascular diseases and liver-related death [3–5].

Little is known about how the incidence of fatal non-AIDS events change with increasing exposure to treatment [6], although several plausible mechanisms have been proposed as to how some adverse effects of cART accumulating over time may contribute to certain non-AIDS conditions [7–9]. For example, use of abacavir, didanosine, indinavir and lopinavir-ritonavir has been reported to be associated with an increased risk of myocardial infarction [10,11] and use of tenofovir, indinavir, atazanavir and lopinavir-ritonavir with risk of chronic kidney disease [12]. However, it is unclear how these risks translate to the patient's long-term prognosis and risk of mortality.

This is a challenging area in HIV research as it is difficult to differentiate potential negative effects received from the use of cART from those that are exacerbated or caused by HIV infection itself and that cART is potentially correcting [13–15]. For example, treatment can reduce the risk of fatal liver-related disease, by increasing CD4 cell count; however, long-term exposure to cART may also result in fatal liver toxicities [16].

Finally non-AIDS-related deaths are a heterogeneous group merging causes of different trends. This may result in a fairly constant rate despite existing dynamic changes within the groups. It is therefore important to divide this group into as many specific categories as possible.

Increased insight into these issues could contribute further to the optimization of cART use, by reducing its harm to an unavoidable minimum and therefore increasing the net benefit.

We therefore investigated the rate of specific causes of death with increasing duration of exposure to cART in the EuroSIDA study after adjustment for potential confounding factors.

Methods

Patients

EuroSIDA is a prospective, observational study of 16 597 HIV-1-infected patients at 103 centres across Europe, Israel and Argentina. Data are collected at clinical sites, extracted and sent to the coordinating centre at 6-monthly intervals. In addition to demographic and clinical information, a complete antiretroviral treatment history is obtained, including dates of starting and stopping each antiretroviral drug, and all CD4 cell count and plasma HIV RNA measurements since last EuroSIDA follow-up. Full details of the study and sample follow-up forms can be found at www.cphiv.dk.

Inclusion criteria

All patients recruited to the EuroSIDA cohort after 1 January 1996 who were on cART at some point whilst under follow-up were included from baseline which was defined as the time of starting cART or enrolment into EuroSIDA, whichever occurred later. In addition all patients were required to have at least one CD4 cell count measurement available at or prior to baseline. Patients were followed until 6 months after their last follow-up visit or until death, whichever occurred first.

Statistical methods

The crude incidence rate of death due to specific causes was calculated per 1000 person years of follow-up (PYFU) stratified by duration of cART exposure [<2, 2–3.99 (reference), 4–5.99, 6–7.99 and >8 years on cART]. cART was defined as receiving three or more antiretrovirals and duration of cART exposure as time actually receiving cART. Any time when the patient was off cART was not counted as exposure time. For patients who were on cART at enrolment into EuroSIDA we were able to reconstruct the length of exposure by obtaining a full ART history.

For individuals who died, date and cause of death are reported by the site investigator and, since 2004, a Coding of Death in HIV (CoDe) case report form is additionally completed for each fatal case and CoDe methods used to determine the underlying cause of death [17]. Deaths reported without a known cause and undetermined by CoDe procedure contribute to approximately 17% of all deaths and are classified by earlier developed method into either unknown AIDS or unknown non-AIDS deaths [18]. Deaths assigned as non-AIDS-related were further classified into non-AIDS-related infection (NARI-death); liver-related (LR-death; deaths due to hepatitis or nonhepatitis liver failure and/or cirrhosis, and liver cancer); non-AIDS-defining malignancies (NADM-death; all malignancies except Kaposi's sarcoma, non-Hodgkin's lymphoma, cervical carcinoma and liver cancer); cardiovascular disease (CVD-death; stroke, myocardial infarction, heart or vascular disease); violent (accidental or violent death, suicide, euthanasia, substance abuse or overdose); other (causes associated with less than 20 deaths); or unknown death (deaths with insufficient information to determine specific non-AIDS cause of death).

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Poisson regression models were fitted for each cause of death separately, adjusting for factors significant ($P < 0.01$) in univariate analysis. Variables investigated were baseline age, sex, ethnic origin, HIV transmission group, region of Europe, smoking status, diabetes, hypertension, hepatitis B (positive status if positive HBV surface antigen test) and C status (positive status if positive hepatitis C antibody test), CD4 cell count, viral load, any previous AIDS-defining illnesses. Year of follow-up was not included in the multivariate model as it was highly correlated with time on cART. However, separate models stratified by date of cART initiation (<2002 and ≥ 2002) were developed. The effect of date of starting cART on the association between exposure to cART and risk of cause-specific death was also investigated using tests for interaction.

We identified a lower risk of death in the first 2 years of exposure to cART; therefore duration of cART exposure was fitted as a continuous variable per year longer on cART from 2 years of exposure onwards. This allowed us to investigate in more detail the effect of long-term exposure to cART.

All analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, North Carolina USA).

Results

A total of 12 069 patients were on cART during follow-up and were included in the analyses; 7194 patients started cART prior to enrolment into the EuroSIDA study and 4875 patients afterwards. The median follow-up time was 5.43 years [interquartile range (IQR) 2.21–9.49] and the median time of exposure to cART was 4.42 years (IQR 2.25–7.17). Table 1 shows baseline characteristics of these patients.

Table 1. Baseline characteristics of patients included into analyses.

Characteristic	Group	Number	Percentage
Patients starting cART in given calendar time period	<2002	6658	55.2
Sex	Male	9007	74.6
Ethnicity	White	10503	88.6
HIV exposure group			
	Homosexual	4899	40.6
	IDU	2679	22.2
	Heterosexual	3539	29.3
Region			
	South	3301	27.3
	West Central	2859	23.7
	North	3005	24.9
	East Central	1478	12.2
	East	987	8.2
	Argentina	439	3.6
Prior AIDS		3818	31.6
Comorbidities			
Hepatitis B			
	Negative	8829	73.1
	Positive	662	5.5
	Unknown	2578	21.4
Hepatitis C			
	Negative	6403	53.0
	Positive	2608	21.6
	Unknown	3058	25.4
Smoking			
	Never	2450	20.3
	Current	4947	41.0
	Previous	2051	17.0
	Unknown	2621	21.7
Hypertension			
	No	3837	31.8
	Yes	1233	10.2
	Unknown	6999	58.0
Diabetes			
	No	10134	84.0
	Yes	282	2.3
	Unknown	1653	13.7
		Median	Interquartile range
Age (years)		38.2	32.8–45.3
CD4 lymphocyte count (cells/μl)	288	162–453	
HIV RNA viral load (log10 copies/ml)	2.84	1.69–4.43	

One hundred and seventeen patients were missing baseline CD4 cell count and 1172 baseline HIV RNA measurement.

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During 70 613 PYFU, 1297 patients died. Around two-thirds of the deaths were due to non-AIDS-related causes (884, 68%). AIDS-related deaths accounted for 413 deaths (32% of all deaths), NARI-death 121 (9%), LR-death 182 (14%), NADM-death 125 (10%), CVD-death 122 (9%), violent death 90 (7%), other death 91 (7%) and 153 (12%) of the non-AIDS death cases remained unknown death [18]. The crude incidence rate of all-cause death, AIDS-related death and non-AIDS-related death were 18.3 [95% confidence interval (CI) 17.4–19.4], 5.85 (5.28–6.41) and 12.5 (11.7–13.3) per 1000 PYFU, respectively.

As shown in Fig. 1, the crude incidence rate of all-cause death decreased with longer exposure to cART, which was largely attributed to a decrease in AIDS-related mortality. The rates of non-AIDS-related death remained fairly constant. After adjustment for confounding variables, including baseline CD4 cell count and HIV RNA, there was a significant decrease in the rate of all-cause and AIDS-related deaths between 2 and 3.99 years and any longer exposure time, but no significant difference in the rate of non-AIDS-related deaths. This was also true for the specific non-AIDS causes, except unknown and violent death for which the risk decreased over time of exposure to cART (Table 2, see detailed models' adjustment in the table footnote).

Figure 2 shows the risk of death stratified by date of starting cART ($<$2002 and $\geq$2002). After adjustment, the risk of all cause, AIDS and non-AIDS-related death in both groups reflected the same trend as observed in the main analyses; however, due to the low number of events it was not possible to further investigate trends for non-AIDS cause-specific deaths.

When time on cART was fitted as continuous variable from 2 years of exposure onwards there was a 5% decrease in the risk of all-cause death [incidence rate ratio (IRR) 0.95, 95% CI 0.92–0.97, $P < 0.0001$] and 14% decrease in the risk of AIDS-related death (IRR 0.86, 95% CI 0.81–0.91, $P < 0.0001$) per one additional year on cART, and a borderline significant decrease in the risk of non-AIDS death (IRR 0.97, 95% CI 0.95–1.00, $P = 0.06$) (Table 3). These findings were consistent while investigating trends from 4 years of exposure onwards.

Of note the risk of non-AIDS death was significantly lower in the first 2 years on cART, which was mostly driven by LR-death and CVD-death (Table 2), and not observed in patients starting cART in 2002 and onwards (Fig. 2).

Sensitivity analyses investigated the incidence rate of cause-specific deaths with cumulative exposure to cART restricting the group of patients to those recruited to the study after 1 January 2002, a period in which there was increasing representation of patients from Eastern Europe. In a separate set of analyses, we also explored the effect of excluding injecting drug users and patients who started cART before enrolment to EuroSIDA. We obtained consistent results, namely no discernable increase in death rate beyond 2–3.99 years of exposure to treatment, although due to lower number of endpoints the confidence intervals were wider (data not shown).

Discussion

The main finding of our study was that there was no evidence of an increase in the risk of any non-AIDS-related death with prolonged exposure to cART. This is, to our knowledge, the first study to look into the association of non-AIDS cause-specific deaths with duration of time actually spent on cART and with a long-term perspective of exposure to treatment. The results are reassuring that so far prolonged use of cART does not appear to be leading to increased risk of death due to some previously identified cumulative effect, or a

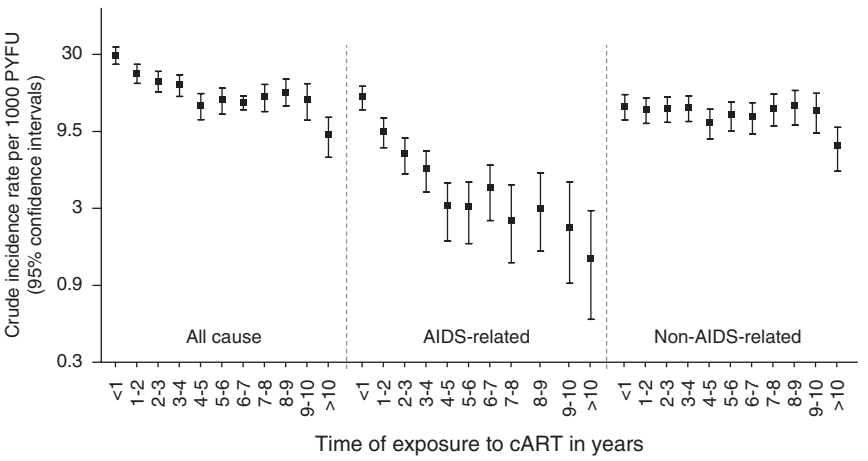

Fig. 1. The crude incidence rate of all-cause, AIDS and non-AIDS-related death by time on cART.

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Table 2. Incidence rate ratios for specific causes of death by cumulative exposure to cART.

Cause of death	Univariate			Multivariate		
All-cause[1]	IRR	95% CI	*P*	IRR	95% CI	*P*
<2	1.33	1.15–1.54	<0.001	1.02	0.88–1.17	0.815
2–3.99	1.00	–	–	1.00	–	–
4–5.99	0.74	0.62–0.88	<0.001	0.78	0.66–0.93	0.006
6–7.99	0.81	0.68–0.98	0.026	0.87	0.72–1.04	0.125
>8	0.69	0.57–0.83	<0.001	0.69	0.57–0.83	<0.001
AIDS death[2]						
<2	2.05	1.61–2.61	<0.001	1.43	1.13–1.81	0.002
2–3.99	1.00	–	–	1.00	–	–
4–5.99	0.51	0.35–0.72	<0.001	0.55	0.38–0.78	<0.001
6–7.99	0.55	0.38–0.80	0.001	0.61	0.42–0.89	0.009
>8	0.34	0.23–0.54	<0.001	0.37	0.24–0.56	<0.001
Non-AIDS[3]						
<2	1.00	0.83–1.21	0.986	0.81	0.67–0.98	0.027
2–3.99	1.00	–	–	1.00	–	–
4–5.99	0.85	0.69–1.04	0.120	0.89	0.73–1.09	0.261
6–7.99	0.88	0.47–1.64	0.682	0.98	0.79–1.21	0.842
>8	0.77	0.41–1.44	0.414	0.84	0.68–1.03	0.099
NARI-death[4]						
<2	1.61	0.99–2.63	0.056	1.17	0.72–1.88	0.523
2–3.99	1.00	–	–	1.00	–	–
4–5.99	0.92	0.52–1.64	0.778	0.99	0.56–1.76	0.977
6–7.99	0.88	0.47–1.64	0.682	0.95	0.51–1.77	0.877
>8	0.77	0.41–1.44	0.414	0.77	0.41–1.44	0.407
LR-death[5]						
<2	0.72	0.47–1.10	0.133	0.56	0.37–0.84	0.005
2–3.99	1.00	–	–	1.00	–	–
4–5.99	0.85	0.56–1.29	0.446	0.89	0.59–1.36	0.605
6–7.99	0.87	0.55–1.35	0.532	0.93	0.60–1.46	0.768
>8	0.61	0.38–0.99	0.046	0.65	0.41–1.06	0.084
NADM-death[6]						
<2	1.31	0.75–2.29	0.333	1.19	0.68–2.07	0.536
2–3.99	1.00	–	–	1.00	–	–
4–5.99	1.14	0.63–2.06	0.663	1.17	0.65–2.12	0.595
6–7.99	1.49	0.83–2.68	0.179	1.52	0.85–2.74	0.159
>8	1.65	0.95–2.88	0.075	1.62	0.93–2.84	0.088
CVD-death[7]						
<2	0.51	0.28–0.94	0.030	0.45	0.25–0.83	0.010
2–3.99	1.00	–	–	1.00	–	–
4–5.99	0.92	0.54–1.56	0.754	0.97	0.57–1.63	0.898
6–7.99	1.01	0.59–1.75	0.963	1.05	0.61–1.80	0.867
>8	1.13	0.68–1.89	0.633	1.11	0.66–1.86	0.680
Violent[8]						
<2	1.00	0.58–1.70	0.991	0.85	0.50–1.46	0.560
2–3.99	1.00	–	–	1.00	–	–
4–5.99	0.63	0.33–1.19	0.156	0.66	0.35–1.24	0.192
6–7.99	0.69	0.35–1.33	0.266	0.72	0.37–1.40	0.333
>8	0.37	0.17–0.82	0.013	0.39	0.17–0.86	0.019
Other[9]						
<2	1.39	0.72–2.71	0.323	1.11	0.58–2.12	0.758
2–3.99	1.00	–	–	1.00	–	–
4–5.99	1.52	0.78–2.97	0.220	1.59	0.81–3.11	0.174
6–7.99	1.62	0.81–3.24	0.174	1.66	0.83–3.33	0.151
>8	1.50	0.76–2.98	0.242	1.46	0.74–2.89	0.278
Unknown[10]						
<2	1.02	0.67–1.54	0.927	0.72	0.48–1.08	0.114
2–3.99	1.00	–	–	1.00	–	–
4–5.99	0.53	0.32–0.89	0.016	0.57	0.34–0.95	0.030
6–7.99	0.63	0.37–1.07	0.090	0.67	0.39–1.13	0.133
>8	0.58	0.35–0.98	0.042	0.56	0.33–0.94	0.027

CI, confidence interval; CVD, cardiovascular disease; IRR, incidence rate ratio; LR, liver-related; NADM, non-AIDS-defining malignancies; NARI, non-AIDS-related infection. Models' adjustment: (1) for sex, ethnic origin, region of Europe, hepatitis B and C (HCV) status, diabetes, hypertension, smoking, viral load (VL), CD4 cell count (CD4), prior AIDS (AIDS) and age; (2) sex, region of Europe (region), HBV, diabetes, hypertension, smoking, viral load,CD4 cell count and prior AIDS; (3) sex, HIV exposure group, ethnic origin, region of Europe, hepatitis B and C status, diabetes, hypertension, smoking, CD4 cell count and age; (4) for HIV exposure group, region of Europe, diabetes, smoking, viral load, CD4 cell count, prior AIDS and age; (5) for HIV exposure group, ethnic origin, region of Europe, hepatitis B and C status, diabetes, hypertensions, smoking, viral load, CD4 cell count, prior AIDS and age; (6) for sex, HIV exposure group, ethnic origin, hepatitis B, diabetes, smoking, viral load, CD4 cell count, prior AIDS and age; (7) for sex HIV exposure group, ethnic origin, hepatitis B and C status, diabetes, hypertension, smoking, viral load, CD4 cell count, prior AIDS and age; (8) for sex, HIV exposure group, hepatitis C status, diabetes, hypertension, smoking, viral load and CD4 cell count; (9) for sex, ethnic origin, region of Europe, hepatitis C status, diabetes, smoking, viral load, CD4 cell count, prior AIDS and age; (10) for sex, HIV exposure group, region of Europe, hepatitis C status, diabetes, hypertension, smoking, viral load, CD4 cell count, prior AIDS and age. All variables as at baseline.

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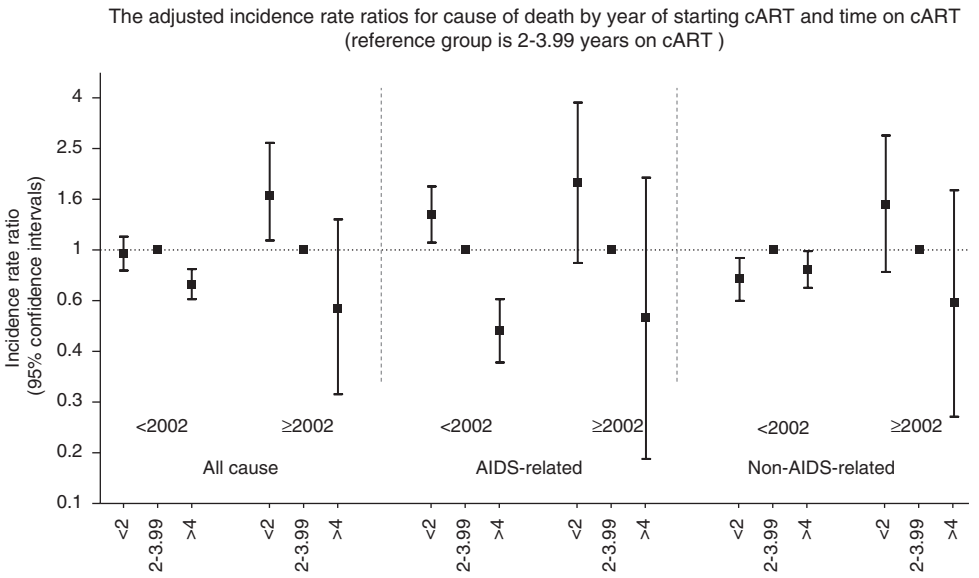

Fig. 2. The incidence rate ratios for cause of death by year of starting cART and time on cART.

drug effect whereby there is a long induction period before disease appears.

Our analyses confirm the prolonged benefit of cART, with a 5% decrease in the overall risk of death per additional year on treatment, which was mostly attributed to a decrease in the risk of AIDS-related death. When non-AIDS cause-specific deaths were investigated contrasting trends for different death causes were evident. For example the risk of LR-death, violent, and unknown death decreased with additional year spent on cART, whereas there was a trend towards an increase in NADM-death. The lower risk of violent death with increasing time on cART could relate to stabilized heath conditions, lifestyle changes or improvement in socio-economic status of those patients who retain in care [19]. The risk of dying from unknown cause also decreased over time spent on cART suggesting that patients sustaining on long-term treatment have more predictable outcomes.

Table 3. The adjusted IRR of cause-specific death by year longer on cART.

Cause of death	IRR	95% CI	*P*
All-cause	0.95	0.92–0.97	<0.001
AIDS	0.86	0.81–0.91	<0.001
Non-AIDS	0.97	0.95–1.00	0.061
NARI-death	0.97	0.90–1.05	0.417
LR-death	0.94	0.89–1.00	0.053
NADM-death	1.07	1.00–1.14	0.056
CVD-death	0.99	0.93–1.06	0.885
Violent death	0.90	0.81–0.99	0.027
Other death	1.01	0.94–1.09	0.725
Unknown death	0.94	0.86–1.01	0.096

CI, confidence interval; CVD, cardiovascular disease; IRR, incidence rate ratio; LR, liver-related; NADM, non-AIDS-defining malignancies; NARI, non-AIDS-related infection. Models' adjustment as in Table 2.

The increase in NADM-death rate may reflect aging of the HIV population, as the effect was no longer present after adjustment for time updated age (data not shown), or improvement in cancer screening. However, it becomes clear that merging all non-AIDS-related deaths in one group might not be sufficient to detect any negative effects of exposure to cART.

Palella *et al.* [20] reported longer time spent on cART to be associated with increased risk of death due to non-AIDS cause. This study did not investigate more specific non-AIDS causes and the majority of patients were less than 4 years on cART. The Antiretroviral Therapy Cohort Collaboration investigated detailed cause-specific mortality rates according to time since first started cART and found the increases in crude incidence rate of NADM-death, CVD-death and LR-death with time since starting cART that was no longer significant after baseline characteristics were taken into account [4]. However, only a limited number of factors were available for model adjustment.

The observed lower risk of non-AIDS death in the first 2 years after treatment initiation, that was more pronounced in patients who started cART prior to 2002 might be due to several potential confounding factors that we were not able to control, for example misclassification of some non-AIDS deaths as AIDS-related deaths or underestimation in the rate of death due to loss to follow-up [21]. However, the rate of loss to follow-up in EuroSIDA is below 5 per 100 PYFU and stable over the study period [22].

A clear advantage of our analyses is that the underlying cause of death is determined based on a standardized

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method of assessing the causal link between a disease or condition and death, namely the Coding Causes of Death in HIV (CoDe) [17]. In addition a separate algorithm classifying all deaths without known causes as either unknown AIDS or unknown non-AIDS-related has been applied, which allowed inclusion of all deaths into our analyses [18].

EuroSIDA is an observational cohort and therefore there may remain unknown or unmeasured confounders that we were unable to adjust for. For example, we were not able to control for the effect of alcohol use or treatment for comorbidities, as this information was not routinely collected through the whole follow-up period. We were also not able to adjust for calendar year of follow-up as it was highly correlated with time on cART, but repeating the models stratifying by year of starting treatment receiving similar results as for the main models. Furthermore, the effect of particular antiretroviral drugs or drug classes on cause-specific mortality could not be investigated due to the low number of events available after such stratification. Since mechanisms of toxicities for individual antiretroviral drugs or drug classes vary significantly they may well have different effects on morbidity and mortality [9,23–25].

As follow-up data accumulate, such analyses will be possible enabling clinicians to compose cART regimens with the optimal risk-benefit ratio for the individual patients [10].

It is important to underline that proper managing of conventional risk factors will prevent developing both cART and non-cART-related metabolic diseases leading to further decrease in many cause-specific deaths [26,27].

It is clear that death due to accumulating treatment toxicities is a very uncommon event. Although we did not find the risk of any specific non-AIDS-related death to increase with prolonged exposure to cART, we cannot at present exclude that such risk may exists for specific sub-groups of patients or individual antiretroviral drugs.

Life-long cART is the current standard of care for HIV-positive people and the duration of cART exposure is only going to continue to increase with improved patient survival. The growing burden of non-AIDS-related comorbidities highlights the need to collect information with longitudinal perspective and continues to focus on the underlying causes of death. Clearly a greater understanding of any risks associated with long-term exposure to cART is needed and future research should further investigate the incidence rates of cause-specific death as an important tool in monitoring overall treatment benefit and long-term drug safety.

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Statistical analysis of the data: J.R, A.M.

Contribution to the writing of the paper: J.D.K., J.R., A.M., P.R., B.L., J.G., A.d'A.M., A.P., J.D.L. O.K.

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The EuroSIDA Study Group: The multicentre study group on EuroSIDA (national coordinators in parenthesis).

Argentina: (M. Losso), C. Elias, Hospital J.M. Ramos Mejia, Buenos Aires. Austria: (N. Vetter), Pulmologisches Zentrum der Stadt Wien, Vienna; R. Zangerle, Medical University Innsbruck, Innsbruck.Belarus: (I. Karpov), A. Vassilenko, Belarus State Medical University, Minsk, V.M. Mitsura, Gomel State Medical University, Gomel; O. Suetnov, Regional AIDS Centre, Svetlogorsk. Belgium: (N. Clumeck), S. De Wit, M. Delforge, Saint-Pierre Hospital, Brussels; R. Colebunders, Institute of Tropical Medicine, Antwerp; L. Vandekerckhove, University Ziekenhuis Gent, Gent. Bosnia-Herzegovina: (V. Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo. Bulgaria: (K. Kostov), Infectious Diseases Hospital, Sofia. Croatia: (J. Begovac), University Hospital of Infectious Diseases, Zagreb.Czech Republic: (L. Machala), D. Jilich, Faculty Hospital Bulovka, Prague; D. Sedlacek, Charles University Hospital, Plzen. Denmark: (J. Nielsen), G. Kronborg, T. Benfield, M. Larsen, Hvidovre Hospital, Copenhagen; J. Gerstoft, T. Katzenstein, A.-B.E. Hansen, P. Skinhøj, Rigshospitalet, Copenhagen; C. Pedersen, Odense University Hospital, Odense; L. Ostergaard, Skejby Hospital, Aarhus. Estonia: (K. Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve. Finland: (M. Ristola), Helsinki University Central Hospital, Helsinki. France: (C. Katlama), Hôpital de la Pitié-Salpétière, Paris; J.-P. Viard, Hôpital Necker-Enfants Malades, Paris; P.-M. Girard, Hospital Saint-Antoine, Paris; J.M. Livrozet, Hôpital Edouard Herriot, Lyon; P. Vanhems, University Claude Bernard, Lyon; C. Pradier, Hôpital de l'Archet, Nice; F. Dabis, D. Neau, Unité INSERM, Bordeaux. Germany: (J. Rockstroh), Universitäts Klinik Bonn; R. Schmidt, Medizinische

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Hochschule Hannover; J. van Lunzen, O. Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; H.J. Stellbrink, IPM Study Center, Hamburg; S. Staszewski, J.W. Goethe University Hospital, Frankfurt; J. Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne. Greece: (J. Kosmidis), P. Gargalianos, G. Xylomenos, J. Perdios, Athens General Hospital; G. Panos, A. Filandras, E. Karabatsaki, 1st IKA Hospital; H. Sambatakou, Ippokration Genereal Hospital, Athens. Hungary: (D. Banhegyi), Szent Lásló Hospital, Budapest. Ireland: (F. Mulcahy), St. James's Hospital, Dublin. Israel: (I. Yust), D. Turner, M. Burke, Ichilov Hospital, Tel Aviv; S. Pollack, G. Hassoun, Rambam Medical Center, Haifa; S Maayan, Hadassah University Hospital, Jerusalem. Italy: (S. Vella), Istituto Superiore di Sanità, Rome; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; C. Arici, Ospedale Riuniti, Bergamo; R. Pristera, Ospedale Generale Regionale, Bolzano; F. Mazzotta, A. Gabbuti, Ospedale S Maria Annunziata, Firenze; V. Vullo, M. Lichtner, University di Roma la Sapienza, Rome; A. Chirianni, E. Montesarchio, M. Gargiulo, Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; G. Antonucci, A. Testa, P. Narciso, C. Vlassi, M. Zaccarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A. Lazzarin, A. Castagna, N. Gianotti, Ospedale San Raffaele, Milan; M. Galli, A. Ridolfo, Osp. L. Sacco, Milan; A. d'Arminio Monforte, Istituto Di Clinica Malattie Infettive e Tropicale, Milan. Latvia: (B. Rozentale), I. Zeltina, Infectology Centre of Latvia, Riga. Lithuania: (S. Chaplinskas), Lithuanian AIDS Centre, Vilnius. Luxembourg: (R. Hemmer), T. Staub, Centre Hospitalier, Luxembourg. Netherlands: (P. Reiss), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. Norway: (V. Ormaasen), A. Maeland, J. Bruun, Ullevål Hospital, Oslo. Poland: (B. Knysz) J. Gasiorowski, Medical University, Wroclaw; A. Horban, E. Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; A. Grzeszczuk, R. Flisiak, Medical University, Bialystok; A. Boron-Kaczmarska, M. Pynka, M. Parczewski, Medical Univesity, Szczecin; M. Beniowski, E. Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H. Trocha, Medical University, Gdansk; E. Jablonowska, E. Malolepsza, K. Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz. Portugal: (F. Antunes), M. Doroana, L. Caldeira, Hospital Santa Maria, Lisbon; K. Mansinho, Hospital de Egas Moniz, Lisbon; F. Maltez, Hospital Curry Cabral, Lisbon. Romania: (D. Duiculescu), Spitalul de Boli Infectioase si Tropicale: Dr Victor Babes, Bucarest. Russia: (A. Rakhmanova), Medical Academy Botkin Hospital, St Petersburg; N. Zakharova, St Petersburg AIDS Centre, St Peterburg; S. Buzunova, Novgorod Centre for AIDS, Novgorod. Serbia: (D. Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. Slovakia: (M. Mokráš), D Staneková, Dérer Hospital, Bratislava. Slovenia: (J Tomazic), University Clinical Centre Ljubljana, Ljubljana. Spain: (J. González-Lahoz), V. Soriano, P. Labarga, J. Medrano, Hospital Carlos III, Madrid; S. Moreno, Hospital Ramon y Cajal, Madrid; B. Clotet, A. Jou, R. Paredes, C. Tural, J. Puig, I. Bravo, Hospital Germans Trias i Pujol, Badalona; J.M. Gatell, J.M. Miró, Hospital Clinic i Provincial, Barcelona; P. Domingo, M. Gutierrez, G. Mateo, M.A. Sambeat, Hospital Sant Pau, Barcelona. Sweden: (A. Karlsson), Venhaelsan-Sodersjukhuset, Stockholm; L. Flamholc, Malmö University Hospital, Malmö. Switzerland: (B. Ledergerber), R. Weber, University Hospital, Zürich; P Francioli, M. Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B. Hirschel, E. Boffi, Hospital Cantonal Universitaire de Geneve, Geneve; H. Furrer, Inselspital Bern, Bern; M. Battegay, L. Elzi, University Hospital Basel. Ukraine: (E. Kravchenko), N. Chentsova, Kiev Centre for AIDS, Kiev; V. Frolov, G. Kutsyna, Luhansk State Medical University; Luhansk; S. Servitskiy, Odessa Region AIDS Center, Odessa; M. Krasnov, Kharkov State Medical University, Kharkov. United Kingdom: (S. Barton), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; A.M. Johnson, D. Mercey, Royal Free and University College London Medical School, London (University College Campus); A. Phillips, M.A. Johnson, A. Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); M. Murphy, Medical College of Saint Bartholomew's Hospital, London; J. Weber, G. Scullard, Imperial College School of Medicine at St. Mary's, London; M. Fisher, Royal Sussex County Hospital, Brighton; C. Leen, Western General Hospital, Edinburgh.

Steering committee: J. Gatell, B. Gazzard, A. Horban, B. Ledergerber, M. Losso, J. Lundgren, A. d'Arminio Monforte, C. Pedersen, A. Phillips, A. Rakhmanova, P. Reiss, M. Ristola, J. Rockstroh (Chair), S. De Wit (Vice-Chair).

Coordinating centre staff: J. Lundgren, O. Kirk, A. Mocroft, A. Cozzi-Lepri, D. Grint, M. Ellefson, D. Podlekareva, J. Kjær, L. Peters, J. Reekie, J. Kowalska, J. Tverland, A.H. Fischer, J. Nielsen.

Conflicts of interest

There are no conflicts of interest.

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