Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population

Alison J. Rodger[a], Rebecca Lodwick[a], Mauro Schechter[b], Steven Deeks[c], Janaki Amin[d], Richard Gilson[a], Roger Paredes[e], Elzbieta Bakowska[f], Frederik N. Engsig[g], Andrew Phillips[a], for the INSIGHT SMART, ESPRIT Study Groups

Background: Due to the success of antiretroviral therapy (ART), it is relevant to ask whether death rates in optimally treated HIV are higher than the general population. The objective was to compare mortality rates in well controlled HIV-infected adults in the SMART and ESPRIT clinical trials with the general population.

Methods: Non-IDUs aged 20–70 years from the continuous ART control arms of ESPRIT and SMART were included if the person had both low HIV plasma viral loads ($\leq$400 copies/ml SMART, $\leq$500 copies/ml ESPRIT) and high $CD4^+$ T-cell counts ($\geq$350 cells/μl) at any time in the past 6 months. Standardized mortality ratios (SMRs) were calculated by comparing death rates with the Human Mortality Database.

Results: Three thousand, two hundred and eighty individuals [665 (20%) women], median age 43 years, contributed 12 357 person-years of follow-up. Sixty-two deaths occurred during follow up. Commonest cause of death was cardiovascular disease (CVD) or sudden death (19, 31%), followed by non-AIDS malignancy (12, 19%). Only two deaths (3%) were AIDS-related. Mortality rate was increased compared with the general population with a $CD4^+$ cell count between 350 and 499 cells/μl [SMR 1.77, 95% confidence interval (CI) 1.17–2.55]. No evidence for increased mortality was seen with $CD4^+$ cell counts greater than 500 cells/μl (SMR 1.00, 95% CI 0.69–1.40).

Conclusion: In HIV-infected individuals on ART, with a recent undetectable viral load, who maintained or had recovery of $CD4^+$ cell counts to at least 500 cells/μl, we identified no evidence for a raised risk of death compared with the general population.

AIDS 2013, **27**:973–979

Keywords: antiretroviral therapy, death rates, HIV, standardized mortality ratio

Introduction

Due to the success of antiretroviral therapies (ART), which have become simpler, less toxic and more effective, mortality in HIV-infected people has declined to such an extent [1–3] that it is now appropriate to investigate if death rates in optimally treated people with persistently undetectable HIV RNA levels (using conventional assays) and high $CD4^+$ T-cell count are actually raised compared with that in the general population. Cohort studies have

[a]University College London, London, UK, [b]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [c]The University of California, San Francisco, San Francisco, California, USA, [d]University of New South Wales, Sydney, New South Wales, Australia, [e]HIV Unit and irsiCaixa AIDS Research Institute, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [f]Wojewodzki Szpital Zakazny, Warsaw, Poland, and [g]Copenhagen University Hospital, Copenhagen, Denmark.

Correspondence to Dr Alison Rodger, Research Department of Infection & Population Health, University College London (UCL), Rowland Hill Street, London NW3 2PF, UK.

Tel: +44 20 7472 6754; fax: +44 20 7794 1224; e-mail: alison.rodger@ucl.ac.uk
Received: 23 September 2012; revised: 1 November 2012; accepted: 15 November 2012.

DOI:10.1097/QAD.0b013e32835cae9c

previously reported that the mortality experience of HIV-infected individuals who start ART and survive the first 6 months continues to be higher than in the general population [4]. However, recent observational cohort studies have also shown that estimated life expectancy for low-risk HIV-infected individuals established on ART who survive the first 6 months after treatment initiation approached that of HIV noninfected individuals [5], and that in a select group of HIV-positive individuals in a French cohort ($CD4^+$ T-cell count $\geq$500 cells/μl), mortality reached the level of the general population after the sixth year of ART [6]. Recent data from a large European collaborative cohort found that mortality rates in male non-IDUs with $CD4^+$ T cells at least 500 cells/μl were similar to the general population [7]. Similar data are also available from developing countries, with one study [8] in four sub-Saharan African countries reporting similar death rates to the general population in individuals who started ART with more than 200 cells/μl and who survived the first year of ART, although in this study the reference rates for mortality for the general population were unlikely to be accurate and loss to follow-up substantial. Further cohort data from Uganda report considerably higher death rates in the HIV-infected population than in Western Europe and North America, but this was comparable to Ugandan data on general population death rates, albeit with substantial variability among patient subgroups [9].

A concern with data from observational cohorts and clinic databases is the degree of completeness of death ascertainment. It is important to study these issues with data from studies in which considerable effort was taken to ascertain vital status. Such was the case in both the Strategies for Management of Antiretroviral Therapy (SMART) and Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) studies [10–12]. The aim of this study was therefore to compare mortality rates in HIV-infected adults with recent or current well controlled HIV [viral load $\leq$400 copies/ml (SMART) or viral load $\leq$500 copies/ml (ESPRIT) and $CD4^+$ T-cell count $\geq$350 cells/μl] with mortality in the general population. For this analysis, we focused on the control arms in each study, as these reflected the now standard-of-care for the management of HIV infection.

Materials and methods

The SMART and ESPRIT study protocols were approved by the institutional review board (IRB) or ethics committee at each clinical site and at the University of Minnesota.

The methods and results of SMART [10] and ESPRIT [11,12] have been published elsewhere. In brief, in SMART, 5472 individuals with $CD4^+$ T-cell counts above 350 cells/μl were enrolled from 318 sites in 33 countries. Individuals were randomized to one of two ART arms: the viral suppression arm involved continuous use of antiretroviral drugs, whereas the drug conservation arm involved $CD4^+$ T-cell guided interruptions of therapy when $CD4^+$ T-cell counts were more than 350 cells/μl and reinitiation of therapy when $CD4^+$ T-cell counts were less than 250 cells/μl. Enrolment was discontinued on 11 January 2006 following the recommendation of the study's independent data and safety monitoring board (DSMB) because of an observed increased risk of opportunistic disease and death in the drug conservation arm compared with the viral suppression arm. ART-experienced individuals in the drug conservation arm were subsequently recommended to reinitiate ART.

The primary endpoint in SMART was the development of new or recurrent opportunistic disease or death from any cause. Using preestablished criteria, an end-point review committee that was unaware of the treatment assignments reviewed the events and classified as opportunistic disease, death from any cause or major cardiovascular, hepatic or renal disease. The end-point review committee classified the underlying cause of death using the Coding of Death in HIV (CoDe) project system (http://www.cphiv.dk/code/tabid/55/default.aspx). A total of 85 deaths were observed, 30 in the viral suppression group (0.8 per 100 person-years).

ESPRIT was a multicentre, international trial. Individuals with $CD4^+$ T-cell count more than 300 cells/μl were randomly assigned, in equal numbers, to receive interleukin-2 along with ART or ART alone. The primary endpoint was new or recurrent HIV disease progression or death. Overall, 4111 individuals (2071 receiving interleukin-2 along with ART and 2040 receiving ART alone) were enrolled. Of those randomized to the control arm, 116 died during follow up.

This analysis included individuals from the continuous ART control arms of SMART and ESPRIT (Fig. 1). Those aged less than 20 or at least 70 years at randomization were excluded, as were IDU individuals. Individual follow-up was included if the person currently had both suppressed viral load ($\leq$400 copies/ml in SMART, $\leq$500 copies/ml in ESPRIT) and $CD4^+$ T-cell count at least 350 cells/μl, or had been in this situation in the past 6 months. Follow-up was censored at the last visit, or at age 70 years.

Standardized mortality ratios (SMRs) were calculated by comparing death rates with those for the general population, stratified by country, age and sex. General population death rates were obtained from the Human Mortality Database (University of California, Berkeley, USA and Max Planck Institute for Demographic Research, Germany; available at www.mortality.org or

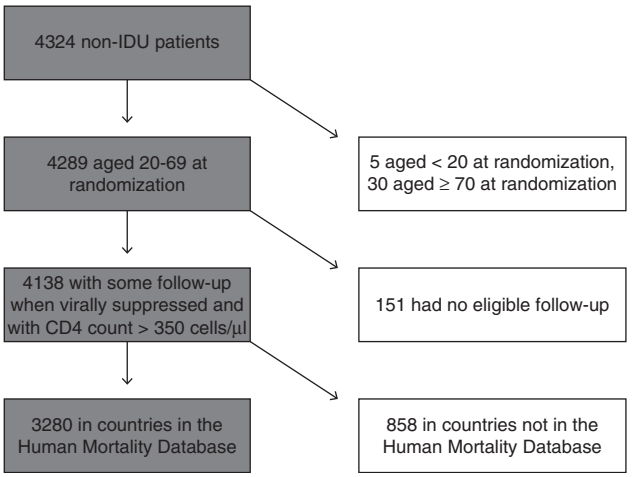

Fig. 1. Flow chart of inclusion of individuals in analysis.

www.humanmortality.de; data downloaded on 24 August 2011). The analysis was restricted to individuals in countries for which such data were available in the Human Mortality Database.

Our main analysis (analysis A) includes follow-up if individuals had had concurrent viral suppression and $CD4^+$ T-cell count of at least 350 cells/μl at some point in the past 6 months. Two additional sensitivity analyses were also conducted, firstly (analysis B) restricting to follow-up in which there is concurrent viral suppression and $CD4^+$ T-cell count of at least 350 cells/μl according to the most recently measured values, and secondly (analysis C) expanding to follow-up in which there has previously been concurrent viral suppression and $CD4^+$ T-cell count of at least 350 cells/μl at any time since enrolment. All *P* values are two-sided and analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

A total of 3280 individuals contributed follow-up time to the analysis, 1971 (60.1%) from SMART and 1309 (39.9%) from ESPRIT (Table 1). Of these, 665 (20.3%) were women and 2615 (79.7%) men. The median age at randomization was 43 years [interquartile range (IQR) 37–50 years]. At randomization, 2516 (76.7%) had a suppressed viral load (≤400 copies/ml SMART, ≤500 copies/ml ESPRIT). The median (IQR) $CD4^+$ T-cell count at randomization was 535 (420–724) cells/μl and the median (IQR) observed nadir $CD4^+$ T-cell count was 228 (120–341) cells/μl. In terms of viral hepatitis coinfections, 4.4% had hepatitis B virus (HBV) infection and 7.7% had hepatitis C virus (HCV) infection. Twenty-five percent had a previous AIDS-defining illness (ADI) prior to randomization. Most individuals were recruited from North America (1746, 53.2%) and Europe (1314, 40.1%). The others were recruited from Australasia (178, 5.4%), Asia (18, 0.6%) and South America (24, 0.7%).

Table 1. Characteristics of the 3280 individuals included in the analysis.

Characteristic	*n* (%)
Trial	
SMART	1971 (60.1)
ESPRIT	1309 (39.9)
Sex	
Female	665 (20.3)
Male	2615 (79.7)
Region	
North America	1746 (53.2)
South America	24 (0.7)
Europe	1314 (40.1)
Asia	18 (0.6)
Australasia	178 (5.4)
Risk group	
MSM	1988 (60.6)
Heterosexual	1075 (32.8)
Blood products / other	90 (2.7)
Unknown	127 (3.9)
Age at randomization	
Median (IQR)	43 (37–50) years
Hepatitis B coinfection[a]	137 (4.4)
Hepatitis C coinfection[b]	237 (7.7)
AIDS prior to randomization	802 (24.5)
Viral load at randomization[c]	
Suppressed[d]	2516 (76.7)
$CD4^+$ T-cell count at randomization	
Median (IQR)	535 (420–724) cells/μl
$CD4^+$ T-cell count nadir before randomization	
Median (IQR)	228 (120–340) cells/μl

IQR, interquartile range.
[a]Missing for 162 (4.9%) individuals.
[b]Missing for 189 (5.8%) individuals.
[c]Missing for six (0.2%) individuals.
[d]Suppressed viral load 400 cells/μl or less for individuals in SMART and 500 cells/μl or less for individuals in ESPRIT.

Individuals contributed a total of 12 357 person-years of eligible follow-up to the main analysis. The median length of follow-up was 3.1 years (IQR 1.9–5.5). Sixty-two deaths occurred during follow-up, giving an overall mortality rate of 5.02 per 1000 person-years [95% confidence interval (CI) 3.85–6.43]. The commonest cause of death was cardiovascular disease (CVD) or sudden death (19, 31%), followed by non-AIDS malignancy (12, 19%), unnatural deaths (accident, suicide or violent death) in 11 cases (18%), non-AIDS and nonhepatitis infection (six, 10%) and liver disease (five, 8%). Only two deaths (3%) were AIDS-related. The cause of death was unknown in one case (2%) (Table 2).

Table 3 shows the observed death rates and SMRs standardized by age and sex and country for the main analysis (A) and the two sensitivity analyses (B) and (C).

Table 2. Documented causes of the 62 deaths in the main analysis.

Cause of death	*n* (%)
AIDS	2 (3%)
Non-AIDS	
CVD or sudden death	19 (31%)
Heart or vascular	2
MI or other ischemic heart disease	4
Stroke	1
Sudden death	3
Found dead	9
Malignancy	12 (19%)
Unnatural deaths	11 (18%)
Accident or other violent death	4
Substance abuse	5
Suicide	2
Infection (nonhepatitis)	6 (10%)
Liver disease	5 (8%)
Chronic viral hepatitis	3
Nonhepatitis liver failure	2
Digestive system disease	2 (3%)
Respiratory system disease	2 (3%)
Chronic obstructive lung disease	1
Other respiratory disease	1
CNS disease	1 (2%)
Haematological disease	1 (2%)
Unknown	1 (2%)
Total	62 (100%)

CVD, cardiovascular disease; CNS, central nervous system.

For the main analysis, 62 deaths were observed in 12 357 years of follow-up, giving an overall SMR of 1.24 (95% CI 0.95–1.59). For individuals with a $CD4^+$ T-cell count between 350 and 499 cells/μl, 28 deaths were observed (against 16 expected) in 3729 years of follow up, indicating that mortality rate was increased compared with the background population (SMR 1.77, 95% CI 1.17–2.55). However, for individuals with $CD4^+$ T-cell counts above 500 cells/μl, no evidence for increased mortality was seen with an SMR of 1.00 (95% CI 0.69–1.40). In the first sensitivity analysis (B), the SMR overall was similar to the background population at 1.00 (95% CI 0.73–1.34). No increased mortality was found in stratification by $CD4^+$ T-cell counts. In the second sensitivity analysis (C) in which the data were not censored on the basis of viral load or $CD4^+$ T-cell counts after meeting our eligibility criteria, we found that overall SMR increased compared with the general population (1.57, 95% CI 1.26–1.94). SMR was also increased in those with $CD4^+$ T-cell count 350–499 cells/μl, but was only marginally above one for $CD4^+$ T-cell count of at least 500 cells/μl (1.22, 95% CI 0.89–1.64). No significant differences in SMR were seen by CD4 nadir count. Overall, in those who had a nadir CD4 cell count less than 200 or more than 200 cells/μl, SMRs were 1.37 (95% CI 0.94–1.92) and 1.13 (95% CI 0.75–1.62), respectively. In those with a current CD4 cell count of more than 500 cells/μl, even when the analysis was restricted to those with nadir CD4 cell count less than 200 cells/μl, the SMR was still close to 1 (SMR 1.18, 95% CI 0.68–1.92).

Discussion

In non-IDU individuals in the continuous ART control arms of the ESPRIT and SMART trials, we identified no evidence for a raised risk of death compared with the general population in HIV-infected individuals on ART, with an undetectable viral load, who maintained or had recovery of $CD4^+$ T-cell counts to at least 500 cells/μl. Comparable mortality rates between select patient groups with well controlled HIV infection and the general population have been previously documented in observational cohort studies from developed and developing countries [5–9]; however, the degree of completeness of ascertainment of deaths data remains a concern with cohort studies and might have resulted in underestimation of death rates. Vital status was unknown for 5.4% of individuals in ESPRIT and 4.2% of individuals in SMART.

Caution is required in interpreting our results due to a number of likely confounders, both measured and unmeasured. Bias could also result because our analysis selects those who enter trials and successfully achieve sustained viral suppression, and a $CD4^+$ T-cell count of at least 500 cells/μl who are likely to be a subset of the population with higher health-seeking behaviour, intervention-adherent behaviour and interest in their own health. They may also have a socioeconomic status different from the general population. However, the broad trial inclusion criteria, the relatively low intensity schedule for individuals and the fact that viral suppression on ART and $CD4^+$ T-cell rise to at least 500 cells/μl has become the norm for most individuals whether in clinical trials or not may limit this bias. In addition, as HIV-infected people tend to be more likely to be smokers than in the general population [13,14] and have other risk behaviours that impact on health such as excess alcohol intake [15] and poorer psychological health [16,17], confounding that could have resulted in a bias in either direction.

However, as the ESPRIT study was initiated in the year 2000, and the SMART study in 2002, many patients were exposed to therapeutic agents with greater toxicities than ART most commonly used in 2012. It is possible that patients initiating ART today have even better long-term outcomes than those observed in the ESPRIT and SMART study cohorts.

Current $CD4^+$ T-cell count (and suppressed HIV viral load) are strong predictors of opportunistic disease as well as other non-AIDS related deaths [1,2,18,19]. In our study, individuals who had current or recent $CD4^+$ T-cell counts above 500 cells/μl had no evidence of increased overall mortality compared with the general population. In contrast, those who had $CD4^+$ T-cell counts between 350 and 499 cells/μl had evidence of higher mortality rates. This is comparable with data from other studies

Table 3. Observed death rates and standardized mortality ratios standardized by age and sex and country for the main analysis (A) and the two sensitivity analyses (B) and (C).

	Overall	Most recent eligible CD4$^+$ T-cell count (cells/μl)	
A[a]		350–499	≥500
Person-years of follow-up	12357	3729	8628
Proportion	100%	30%	70%
Observed deaths	62	28	34
Expected deaths	49.82	15.86	33.96
SMR (95% CI)	1.24 (0.95–1.59)	1.77 (1.17–2.55)	1.00 (0.69–1.40)
B[a]		350–499	≥500
Person-years of follow-up	11 005	3012	7993
Proportion	100%	27%	73%
Observed deaths	44	16	28
Expected deaths	44.07	12.67	31.40
SMR (95% CI)	1.00 (0.73–1.34)	1.26 (0.72–2.05)	0.89 (0.59–1.29)
C[a]			
Person-years of follow-up	13 787	4391	9396
Proportion	100%	32%	68%
Observed deaths	87	42	45
Expected deaths	55.41	18.60	36.81
SMR (95% CI)	1.57 (1.26–1.94)	2.26 (1.63–3.05)	1.22 (0.89–1.64)

CI, confidence interval; SMR, standardized mortality ratio.
[a](A) Main analysis includes follow-up on individuals who had concurrent viral suppression and CD4$^+$ T-cell count of at least 350 cells/μl at some point in the past 6 months. (B) Sensitivity analysis restricted to include only follow-up wherein there is concurrent viral suppression and CD4$^+$ T-cell count of at least 350 cells/μl. (C) Sensitivity analysis expanded to include all follow-up wherein there has previously been concurrent viral suppression and CD4$^+$ T-cell count of at least 350 cells/μl at any time since enrolment.

demonstrating that CD4$^+$ T-cell count remains a dominant prognostic factor for mortality among HIV-infected individuals even as time on ART increases [20] and even among those with viral load suppression. French cohort data also showed that achieving a CD4$^+$ T-cell count of 500 cells/μl was associated with the same rates of mortality as among the general population after 6 years after ART, whereas among individuals with a CD4$^+$ T-cell count between 350 and 499 cells/μl, mortality remained higher than in the general population [6]. Our data support the importance of early diagnosis and treatment to improve clinical outcomes, and it is likely that much of the excess mortality associated with HIV would be preventable with timely diagnosis of HIV and initiation of ART [21]. In individuals who start ART at a CD4$^+$ T-cell count less than 200 cells/μl, full reconstitution and normalization of CD4$^+$ T-cell count above 500 cells/μl is unlikely to be achieved even after several years of ART therapy [20,22]. In addition, optimizing individual patient responses to ART is vital through addressing factors that affect adherence and developing effective interventions to improve adherence and therefore long-term outcomes [23].

An important clinical question currently is whether people with HIV and CD4$^+$ T-cell count above 350 cells/μl should initiate therapy immediately or defer until the CD4$^+$ T-cell count is around 350 cells/μl. Absolute risks of serious events and death are low in such people, whether on ART or not. A similar analysis to that presented here has previously been reported from a cohort, which focussed on ART-naive people with high CD4$^+$ T-cell count. In MSM with CD4$^+$ T-cell count above 500 cells/μl, there was no evidence of increased risk compared with the general population [24]. The balance of the risks and benefits of starting ART in this group is likely to be too fine to be reliably determined on the basis of data from observational studies and analyses, such as the one we present here. It needs to be assessed in randomized trials, such as the ongoing START trial, which is randomizing people with CD4$^+$ T-cell count at least 500 cells/μl, to immediate ART versus deferral to CD4$^+$ T-cell count reaching 350 cells/μl [25].

The role of chronic inflammation in driving disease in treated adults has been a strong focus of investigators working with the SMART and ESPIRIT cohorts. These studies have consistently found that markers of inflammation [e.g. interleukin (IL)-6 and sCD14] and coagulation (D-dimers) are elevated among treated individuals (as compared with well matched uninfected adults) and strongly associated with subsequent morbidity and mortality [26]. Moreover, there have been limited associations between the proximal CD4$^+$ T cells and inflammation/coagulation markers in these studies. These data collectively suggest that mechanistic pathways not captured by viral load and CD4$^+$ T-cell count data might contribute to higher than expected morbidity and mortality in treated individuals. On the basis of these observations, it might be expected that inflammation might remain elevated among individuals who have maintained viral suppression and high CD4$^+$ T-cell counts (≥500 cells/μl) and that this might predict excess disease. Of note, emerging data from the study of human ageing suggest that the cumulative harm associated with persistently low-level inflammation may only become

apparent as people enter their sixth and later decades of life [27]. It remains a distinct possibility that excess morbidity and mortality among optimally treated adults may hence only become apparent as the current generation of treated HIV-infected individuals age.

Few deaths were directly related to HIV in our study. The commonest cause of death was CVD or sudden death, followed by non-AIDS malignancies. The impact of chronic viral hepatitis was also evident and reflects the increased contribution of this to mortality in the post-ART era, although our study excluded IDUs who remain the group most at risk of viral hepatitis coinfection [28]. Suicide and accident or other violent death were also apparent and may reflect the recognized increased prevalence of poor psychological health and mental health disorders in the HIV-infected population compared with the background population, although this most frequently affects HIV-infected persons who are also IDUs [16,17].

Further study limitations include that power is limited by the person time and number of deaths observed in the two studies. Finally, our primary analysis in which follow-up was not censored 6 months after loss of virus control or a decline in $CD4^+$ T-cell counts may have resulted in exclusion of meaningful events; some individuals stop therapy or become less adherent as they develop significant morbidity, which could have resulted in exclusion of their follow-up when they died, and hence also of their death. Also, many chronic diseases such as cancer result in decline in $CD4^+$ T-cell counts, which raises concerns that the overall health of treated adults may be less robust than that indicated in our primary analysis. However, even in our analysis in which no censoring was used, the SMR was still not markedly above 1 (1.22, 95% CI 0.89–1.64).

In conclusion, we found using data from the SMART and ESPRIT randomized controlled trials (RCTs) that in (non-IDU) HIV-infected individuals on ART, with an undetectable viral load, who maintained or had recovery of $CD4^+$ T-cell counts to at least 500 cells/μl, there was no evidence for a raised risk of death compared with the general population.

Acknowledgements

We wish to thank the SMART and ESPRIT participants. S.D. is supported by grant K24AI069994.

A.J.R. was involved in analysis design, data interpretation, wrote the first draft of the manuscript and wrote the final version of the article. R.L. performed all analyses, interpreted the data and helped draft the manuscript. A.P. developed the concept and was involved in analysis design, data interpretation and had substantive input into manuscript drafting and is the overall guarantor. M.S., S.D., J.A., R.G., R.P., E.B. and F.N.E. contributed to data acquisition and management. M.S. and S.D. also had substantive input into manuscript drafting. All members of the writing committee participated in discussions on analysis design, interpretation of the findings and critically reviewed the manuscript.

This work was funded by NIH Grants U01-AI068641, U01-AI46957, U01-AI046362 and U01-AI042170.

A list of investigators in SMART is given in Ref. [10] and a list of investigators in ESPRIT is given in Ref. [11].

Conflicts of interest

A.J.R., R.L., M.S., S.D., J.A., R.G., R.P., E.B., F.N.E. and A.P. have no conflicts of interest to declare.

References

1. Keiser O, Taffé P, Zwahlen M, Battegay M, Bernasconi E, Weber R, *et al.*, the Swiss HIV Cohort Study. **All-cause mortality in the Swiss HIV Cohort Study from 1990 to 2001 in comparison with the Swiss population.** *AIDS* 2004; **18**:1835–1843.
2. May M, Gompels M, Delpech V, Porter K, Post F, Johnson M, *et al.* **Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study.** *BMJ* 2011; **343**:d6016.
3. Zwahlen M, Harris R, May M, Hogg R, Costagliola D, de Wolf F, *et al.*, for the Antiretroviral Therapy Cohort Collaboration. **Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries.** *Int J Epidemiol* 2009; **38**:1624–1633.
4. The Antiretroviral Therapy Cohort Collaboration. **Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries.** *Int J Epidemiol* 2009; **38**:1624–1633.
5. van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F, **ATHENA national observational cohort study. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals.** *AIDS* 2010; **24**: 1527–1535.
6. Lewden C, Chene G, Morlat P, Raffi F, Dupon M, Dellamonica P, *et al.* **HIV-infected adults with a CD4 cell count greater than 500 cells/mm^3 on long-term combination antiretroviral therapy reach same mortality rates as the general population.** *J Acquir Immune Defic Syndr* 2007; **46**:72–77.
7. Lewden C, Bouteloup V, De Wit S, Sabin C, Mocroft A, Wasmuth JC, *et al.* **for The Collaboration of Observational HIV Epidemiological Research Europe (COHERE). All-cause mortality in treated HIV-infected adults with CD4 ≥500/mm^3 compared with the general population: evidence from a large European observational cohort collaboration.** *Int J Epidemiol* 2012; **41**:433–445.
8. Brinkhof MW, Boulle A, Weigel R, Messou E, Mathers C, Orrell C, *et al.*, International Epidemiological Databases to Evaluate AIDS (IeDEA). **Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality.** *PLoS Med* 2009; **6**:e1000066.
9. Mills EJ, Bakanda C, Birungi J, Chan K, Ford N, Cooper CL, *et al.* **Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda.** *Ann Intern Med* 2011; **155**:209–216.
10. The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. **$CD4^+$ count guided interruptions of antiretroviral therapy.** *N Engl J Med* 2006; **355**:2283–2296.

11. Abrams D, Lévy Y, Losso MH, Babiker A, Collins G, Cooper DA, *et al*., for the INSIGHT-ESPRIT Study Group; SILCAAT Scientific Committee. **Interleukin-2 therapy in patients with HIV infection.** *N Engl J Med* 2009; **361**:1548–1559.
12. Emery S, Abrams DI, Cooper DA, Darbyshire JH, Lane HC, Lundgren JD, *et al*., for the ESPRIT Study Group. **The evaluation of subcutaneous proleukin (interleukin-2) in a randomized international trial: rationale, design, and methods of ESPRIT.** *Control Clin Trials* 2002; **2**:198–220.
13. Bénard A, Tessier JF, Rambeloarisoa J, Bonnet F, Fossoux H, Neau D, *et al*. **HIV infection and tobacco smoking behaviour: prospects for prevention? ANRS CO3 Aquitaine Cohort, 2002.** *Int J Tuberc Lung Dis* 2006; **10**:378–383.
14. Friis-Møller N, Weber R, Reiss P, Thiébaut R, Kirk O, d'Arminio Monforte A, *et al*. **Cardiovascular disease risk factors in HIV patients – association with antiretroviral therapy. Results from the DAD study.** *AIDS* 2003; **17**:1179–1193.
15. Galvan FH, Bing EG, Fleishman JA, London AS, Caetano R, Burnam MA. **The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study.** *J Stud Alcohol* 2002; **63**:179–186.
16. Weiser SD, Wolfe WR, Bangsberg DR. **The HIV epidemic among individuals with mental illness in the United States.** *Curr HIV/AIDS Rep* 2004; **1**:186–192.
17. Bing EG, Burnam MA, Longshore D, Fleishman JA, Sherbourne CD, London AS, *et al*. **Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States.** *Arch Gen Psychiatry* 2001; **58**:721–728.
18. Lanoy E, May M, Mocroft A, Phillip A, Justice A, Chêne G, *et al*., for the Antiretroviral therapy cohort collaboration (ART-CC). **Prognosis of patients treated with cART from 36 months after initiation, according to current and previous CD4 cell count and plasma HIV-1 RNA measurements.** *AIDS* 2009; **23**:2199–2208.
19. Phillips AN, Neaton J, Lundgren JD. **The role of HIV in serious diseases other than.** *AIDS* 2008; **22**:2409–2418.
20. Moore RD, Keruly JC. **CD4 cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression.** *Clin Infect Dis* 2007; **44**:441–446.
21. Nakagawa F, Lodwick RK, Smith CJ, Smith R, Cambiano V, Lundgren JD, *et al*. **Projected life expectancy of people with HIV according to timing of diagnosis.** *AIDS* 2012; **26**:335–343.
22. Nash D, Katyal M, Brinkhof MW, Keiser O, May M, Hughes R, *et al*., for the ART-LINC Collaboration of IeDEA. **Long-term immunologic response to antiretroviral therapy in low-income countries: a collaborative analysis of prospective studies.** *AIDS* 2008; **22**:2291–2302.
23. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. **The impact of adherence on CD4 cell count responses among HIV-infected patients.** *J Acquir Immune Defic Syndr* 2004; **35**:261–268.
24. Study Group on Death Rates at High CD4 Count in Antiretroviral Naive Patients. **Death rates in HIV-positive antiretroviral-naive patients with CD4 count greater than 350 cells per μL in Europe and North America: a pooled cohort observational study.** *Lancet* 2010; **376**:340–345.
25. INSIGHT START Study Group. **Considerations in the rationale, design and methods of the Strategic Timing of AntiRetroviral Treatment (START) study.** *Clin Trials* 2012. [Epub ahead of print]
26. Neuhaus J, Jacobs DR Jr, Baker JV, Calmy A, Duprez D, La Rosa A, *et al*. **Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection.** *J Infect Dis* 2010; **201**:1788–1795.
27. De Martinis M, Franceschi C, Monti D, Ginaldi L. **Inflamm-ageing and lifelong antigenic load as major determinants of ageing rate and longevity.** *FEBS Lett* 2005; **579**:2035–2039.
28. Koziel MJ, Peters MG. **Viral hepatitis in HIV infection.** *N Engl J Med* 2007; **356**:1445–1454.