



Online article and related content  
current as of July 21, 2008.

## Changes in the Risk of Death After HIV Seroconversion Compared With Mortality in the General Population

Krishnan Bhaskaran; Osamah Hamouda; Mette Sannes; et al.

*JAMA*. 2008;300(1):51-59 (doi:10.1001/jama.300.1.51)

<http://jama.ama-assn.org/cgi/content/full/300/1/51>

Correction

[Contact me if this article is corrected.](#)

Citations

[This article has been cited 2 times.](#)  
[Contact me when this article is cited.](#)

Topic collections

Substance Abuse/ Alcoholism; Infectious Diseases; HIV/AIDS; Prognosis/  
Outcomes; Public Health  
[Contact me when new articles are published in these topic areas.](#)

Subscribe

<http://jama.com/subscribe>

Permissions

[permissions@ama-assn.org](mailto:permissions@ama-assn.org)  
<http://pubs.ama-assn.org/misc/permissions.dtl>

Email Alerts

<http://jamaarchives.com/alerts>

Reprints/E-prints

[reprints@ama-assn.org](mailto:reprints@ama-assn.org)

# Changes in the Risk of Death After HIV Seroconversion Compared With Mortality in the General Population

Krishnan Bhaskaran, MSc

Osamah Hamouda, MD

Mette Sannes, MLabTech

Faroudy Boufassa, MD

Anne M. Johnson, MD

Paul C. Lambert, PhD

Kholoud Porter, PhD

for the CASCADE Collaboration

**A** NUMBER OF STUDIES HAVE REPORTED the dramatic decreases in mortality among individuals infected with human immunodeficiency virus (HIV) since the widespread introduction of highly active antiretroviral therapy (HAART) in industrialized countries.<sup>1,2</sup> It is important to provide up-to-date and robust estimates of expected mortality as anti-HIV drugs and strategies continue to improve. Such estimates help policy makers and those planning health care to monitor the effectiveness of treatments at a population level and provide an indicator of the ongoing and likely future impact of HIV disease on health care needs.

With mortality among HIV-infected individuals decreasing to relatively low levels compared with the pre-HAART era and with patients living to older ages, it is also of increasing interest to assess how mortality rates of HIV-infected individuals compare with those of the general uninfected population, ie, the "excess mortality."<sup>3</sup> Overall mortality of HIV-infected individuals is likely to be increasingly influenced by deaths that would have occurred regardless of HIV

**Context** Mortality among human immunodeficiency virus (HIV)-infected individuals has decreased dramatically in countries with good access to treatment and may now be close to mortality in the general uninfected population.

**Objective** To evaluate changes in the mortality gap between HIV-infected individuals and the general uninfected population.

**Design, Setting, and Population** Mortality following HIV seroconversion in a large multinational collaboration of HIV seroconverter cohorts (CASCADE) was compared with expected mortality, calculated by applying general population death rates matched on demographic factors. A Poisson-based model adjusted for duration of infection was constructed to assess changes over calendar time in the excess mortality among HIV-infected individuals. Data pooled in September 2007 were analyzed in March 2008, covering years at risk 1981-2006.

**Main Outcome Measure** Excess mortality among HIV-infected individuals compared with that of the general uninfected population.

**Results** Of 16 534 individuals with median duration of follow-up of 6.3 years (range, 1 day to 23.8 years), 2571 died, compared with 235 deaths expected in an equivalent general population cohort. The excess mortality rate (per 1000 person-years) decreased from 40.8 (95% confidence interval [CI], 38.5-43.0; 1275.9 excess deaths in 31 302 person-years) before the introduction of highly active antiretroviral therapy (pre-1996) to 6.1 (95% CI, 4.8-7.4; 89.6 excess deaths in 14 703 person-years) in 2004-2006 (adjusted excess hazard ratio, 0.05 [95% CI, 0.03-0.09] for 2004-2006 vs pre-1996). By 2004-2006, no excess mortality was observed in the first 5 years following HIV seroconversion among those infected sexually, though a cumulative excess probability of death remained over the longer term (4.8% [95% CI, 2.5%-8.6%] in the first 10 years among those aged 15-24 years).

**Conclusions** Mortality rates for HIV-infected persons have become much closer to general mortality rates since the introduction of highly active antiretroviral therapy. In industrialized countries, persons infected sexually with HIV now appear to experience mortality rates similar to those of the general population in the first 5 years following infection, though a mortality excess remains as duration of HIV infection lengthens.

*JAMA.* 2008;300(1):51-59

www.jama.com

infection, and mortality in the general uninfected population provides a natural reference point for taking this into account. This concept has been used in

studies of other diseases in which successfully treated patients frequently live for many years, such as Hodgkin disease<sup>4</sup> and thyroid<sup>5</sup> and other<sup>6</sup> cancers.

**Author Affiliations:** Medical Research Council Clinical Trials Unit, London, United Kingdom (Mr Bhaskaran and Dr Porter); Robert Koch Institute, Berlin, Germany (Dr Hamouda); Ullevål University Hospital, Oslo, Norway (Ms Sannes); INSERM U822, Hôpital Bicêtre, Paris, France (Dr Boufassa); University College London, London, United Kingdom (Dr Johnson); and

University of Leicester, Leicester, United Kingdom (Dr Lambert).

**Members of the CASCADE Collaboration** are listed at the end of this article.

**Corresponding Author:** Kholoud Porter, PhD, MRC Clinical Trials Unit, 222 Euston Rd, London NW1 2DA, United Kingdom (kp@ctu.mrc.ac.uk).

A few studies have compared HIV-infected and uninfected populations in industrialized countries, reporting reductions in the standardized mortality ratio in the early years of HAART availability<sup>7</sup> and estimating a reduced life expectancy of 17 years for HIV-infected individuals compared with that of the uninfected population.<sup>8</sup> Two further studies specifically considering those with a good initial response to treatment found an increased mortality risk, even in this subgroup.<sup>9,10</sup>

These studies have not been able to adjust for duration of HIV infection, which is a key factor influencing mortality risk and could confound other relationships. Using a large data set of individuals with well-estimated HIV seroconversion dates—thus avoiding biases that can occur when duration of infection is unknown<sup>11</sup>—we aimed to evaluate changes over calendar time in the excess mortality of HIV-infected individuals compared with expected mortality in the general uninfected population, adjusting for duration of HIV infection. We further aimed to assess changes over calendar time in the effects of prognostic factors and in the overall and excess probability of death at various stages of HIV infection. We also report corresponding changes over time in the uptake and use of HAART in our population.

## METHODS

Data were used from CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe), which has been described elsewhere.<sup>12</sup> It is currently a collaboration of 23 cohorts of individuals with well-estimated dates of HIV seroconversion from Europe (20 cohorts from Denmark [1], France [4], Germany [1], Greece [1], Italy [1], the Netherlands [2], Norway [2], Spain [4], Switzerland [1], and the United Kingdom [3]), Australia (2 cohorts), and Canada (1 cohort). All eligible individuals are recruited, both prospectively and retrospectively, to the constituent cohorts through the clinical centers where they receive their HIV care, and an enrollment date is re-

corded for each participant. Of the 23 cohorts, 3 regional and 6 national cohorts collect data on individuals from a number of HIV clinical centers across the region or country, through the abstraction of medical records for all participants from routine clinic visits. These data are recorded on clinic report forms and then entered into the individual cohort database. Data are then extracted according to an agreed-on standardized data exchange protocol and submitted to the CASCADE coordinating center (Medical Research Council Clinical Trials Unit, London, United Kingdom) on an annual basis, where they are pooled. The remaining 14 single-clinic cohorts abstract data directly from their clinic database according to the same standardized data exchange protocol and forward the data to the coordinating center. Enrollment averaged 317 individuals per year overall from 1985-1987 and increased to 801 per year over the 19-year period 1988-2006. Six cohorts included in the analysis had ceased recruitment of new seroconverters in 1992, 1997 (2 cohorts), 2000, 2002, and 2004. These 6 cohorts make up 7.7% of data included in the analyses. A subgroup of participants represented by the UK cohort data presented herein were evaluated in a previous study estimating changes in survival over calendar time after HIV seroconversion in a UK setting.<sup>13</sup>

All cohorts received approval from their individual ethics review boards except for the Danish cohort, which received approval from the National Data Registry Surveillance Agency because Danish law allowed collection and pooling of anonymized clinical data with approval from this agency alone. Two ethics review boards deemed their cohort participants exempt from providing signed informed consent. Signed informed consent was obtained from all others. Approval was also given by all ethics review boards to pool anonymized data for analyses and dissemination.

Estimates of HIV seroconversion dates are accurate to within 18, 12, and

6 months for 100%, 87%, and 63% of individuals, respectively, and are based on documented evidence of seroconversion. In 95% of cases, this evidence comprised a documented negative HIV antibody test result, which must be dated fewer than 3 years before the first positive result, and seroconversion date is estimated as the midpoint between the last negative and first positive test results. For the remaining 5% of cases, alternative documented laboratory evidence of seroconversion is available (real-time polymerase chain reaction positivity in the absence of HIV antibodies, or antigen positivity with <4 bands on a Western blot).

We included all individuals 15 years or older at seroconversion who had sexual or injection drug use (IDU) exposure to HIV and at least 1 day of follow-up since enrollment into the cohort. Individuals infected through hemophilia treatment (n=234) and occupational exposure (n=156) were excluded, as were 547 with unknown exposure type. To avoid survivorship bias, late-entry methods were used so that, in cases in which seroconversion was identified retrospectively, time since seroconversion was only considered "at risk" from the date of enrollment into the cohort. Data were pooled in September 2007 and analyzed in March 2008, with follow-up available from May 1981 to June 2007. Follow-up time was censored on the date at which mortality data were assumed to be complete for each contributing cohort; death registration is compulsory in all countries represented in CASCADE, and for 14 of the 21 cohorts represented in the final analysis there is active cross-checking with national death registers for individuals lost to follow-up. As a further measure to avoid underascertainment of death due to reporting delays, we applied additional right-censoring on December 31, 2006.

## Statistical Analysis

Changes over time in the overall risk of death were calculated from a Cox model stratified by cohort and ad-

justed for age at seroconversion, sex, and HIV exposure category, with calendar period of follow-up as a time-updated covariate, categorized to represent the era before extensive availability of HAART (pre-1996) and at regular intervals thereafter (1996-1997, 1998-1999, 2000-2001, 2002-2003, and 2004-2006). We confirmed that there was no evidence against the proportional hazards assumption by a test based on the Schoenfeld residuals, where  $P < .05$  would indicate problems with the assumption.<sup>14</sup>

For the analysis of excess mortality, the expected number of deaths was calculated by applying annual probability of death data from the general population to the study population, considering individuals to be at risk until their actual date of death or censoring.<sup>15</sup> The general population mortality data were obtained from the Human Mortality Database in July 2007,<sup>16</sup> stratified by age, sex, calendar year at risk, and country, and were matched to the study population on these factors. Race and ethnicity were not reported. The number of deaths among CASCADE individuals in each demographic stratum was then modeled using a Poisson process, offsetting the expected deaths. This is known as a relative survival model and provides adjustment for background mortality without the need for information on cause of death.<sup>3</sup> Time since seroconversion was divided into 1-year intervals and included in the model as a categorical variable,<sup>17</sup> thus effectively assuming a piecewise constant hazard of excess mortality in each 1-year interval following seroconversion. To check the sensitivity of our results to this assumption, we also repeated our analyses using 3-month and 6-month intervals in the first 2 years of infection, thus allowing the hazard function more flexibility close to seroconversion.

Within this relative survival model framework, we examined changes in the risk of excess mortality over calendar time of follow-up (time-updated), adjusting for age at seroconversion, sex, and HIV exposure category. The rela-

tive survival models provide estimates of excess hazard ratios (eHRs), the interpretation of which is similar to that of the familiar Cox hazard ratio. For example, an eHR of 1.5 for male/female would indicate that males have a 50% higher risk of dying compared with females, after accounting for expected background mortality. We then investigated the effects of age at seroconversion, sex, and HIV exposure category as potential prognostic factors for excess mortality. Interactions with calendar time were added to assess whether these effects had changed over calendar time. Two-sided  $P$  values for individual model parameters and interactions were produced using likelihood ratio tests of nested models, and for model-building purposes we considered  $P < .05$  to indicate statistical significance.

Using subgroups based on the most important factors from the final model, we then calculated life-table estimates of the cumulative survival and relative survival function<sup>18</sup> by duration of infection in each calendar period, by multiplying interval-specific probabilities. Hence the corresponding cumulative overall (1 – cumulative survival) and excess (1 – relative survival) probability of death at 5, 10, and 15 years of HIV infection duration were derived (as preplanned analyses). These intervals were chosen because we anticipated that reliable estimates could be derived up to 15 years from HIV seroconversion (in a prior report, stable estimates of overall survival to 10 years following HIV seroconversion were generated,<sup>1</sup> and 5 additional years of follow-up data are now available), and we wished to describe changes in mortality patterns and allow comparison across subgroups at a small number of regular intervals of infection duration. Additional late entry and censoring were applied at the beginning and end, respectively, of the calendar period in question; thus, estimates for each period covered the entire duration of infection (incorporating short-term information from the recently diagnosed individuals and longer-term in-

formation from those diagnosed in the past). This approach is known as period analysis and has been commonly used in population-based studies.<sup>1,19</sup>

Finally, in the same calendar periods, we described the time to starting HAART (defined as at least 3 antiretroviral drugs representing at least 2 drug classes or including abacavir or tenofovir<sup>20</sup>) using Kaplan-Meier methods and the proportion of time spent receiving HAART. The numerator for the latter was the amount of person-time spent receiving HAART as derived from the prescription start and stop dates recorded for individual drugs during routine clinical follow-up. Because therapy guidelines recommend the initiation of HAART before CD4 cell count decreases to 200 cells/ $\mu$ L and HAART is typically initiated at 200 to 350 cells/ $\mu$ L,<sup>20,21</sup> we considered as the denominator only time at risk after the first CD4 cell count below 350 cells/ $\mu$ L or after HAART initiation, whichever came earlier.

All statistical analyses were performed using Stata version 10 (Stata-Corp, College Station, Texas).

## RESULTS

### Participants

The analysis included 16 534 individuals (TABLE 1) with median age at HIV seroconversion of 29 years (interquartile range [IQR], 24-36 years). The reported exposure category was sex between males for 9465 individuals (57%), IDU for 3047 (18%), and sex between males and females for 4022 (24%). For year of seroconversion, the median was 1994 (range, 1980-2006). The study observation time ranged from May 1981 to December 2006, and all but 1 cohort (representing 0.5% of the data) contributed data to every calendar period considered in the analysis. The median duration of follow-up was 6.3 years (range, 1 day to 23.8 years), with 16 344 individuals (99%) having more than 1 month of follow-up. There were 21 cohorts represented in the final included data (after excluding 2 with only hemophilia patients), with 16 143 individuals (98%) belonging to European cohorts. The median num-

ber of individuals included per cohort was 388 (range, 56-7000). For 2 contributing cohorts the reported exposure category was exclusively IDU and for 1 cohort was exclusively sex between males; however, most individuals (16 256 [98%]) were enrolled in cohorts covering all 3 exposure categories.

### Changes Throughout Calendar Time in Excess Mortality Risk and Prognostic Factors

A total of 2571 individuals had died as of December 2006, compared with an estimated 235 deaths that would have been expected in a matched general population cohort (TABLE 2). The excess mortality rate per 1000 person-years was 40.8 (95% confidence interval [CI], 35.8-43.0; 1275.9 excess deaths in 31 302 per-

son-years) pre-1996, decreasing in each subsequent calendar period to 6.1 (95% CI, 4.8-7.4; 89.6 excess deaths in 14 703 person-years) in 2004-2006.

The overall adjusted hazard ratio of death compared with pre-1996 was 0.57 (95% CI, 0.51-0.64), 0.20 (95% CI, 0.18-0.24), 0.15 (95% CI, 0.12-0.17), 0.13 (95% CI, 0.11-0.15), and 0.09 (95% CI, 0.07-0.11) in 1996-1997, 1998-1999, 2000-2001, 2002-2003, and 2004-2006, respectively. In the relative survival model adjusted for background mortality, as well as duration of infection and prognostic factors, the eHR of death compared with pre-1996 was 0.54 (95% CI, 0.48-0.60), 0.17 (95% CI, 0.14-0.20), 0.12 (95% CI, 0.10-0.14), 0.10 (95% CI, 0.08-0.12), and 0.06 (95% CI, 0.05-0.08) in the

same periods, respectively. Older age at seroconversion was associated with a higher risk of excess mortality (eHR, 2.54; 95% CI, 2.10-3.07 for age  $\geq$ 45 years compared with age 15-24 years;  $P < .001$ ), as was a reported exposure category of IDU (eHR, 1.52; 95% CI, 1.36-1.69 [ $P < .001$ ] compared with sex between males). Females appeared to be at lower risk than males (eHR, 0.80; 95% CI, 0.70-0.91 [ $P = .001$ ]).

There was strong evidence for a change over calendar time in the effects of age at seroconversion ( $P = .002$ ), exposure category ( $P < .001$ ), and sex ( $P < .001$ ) when these interactions were added individually to our model, although when all 3 were added, only the exposure category interaction remained statistically significant

**Table 1.** Characteristics of the Study Population

Characteristic	No. (%) by Calendar Period						Total
	Pre-1996	1996-1997	1998-1999	2000-2001	2002-2003	2004-2006	
Total No. seroconverting	9500	1615	1338	1446	1480	1155	16 534
Sex							
Male	7365 (78)	1271 (79)	1031 (77)	1160 (80)	1169 (79)	975 (84)	12 971 (78)
Female	2135 (22)	344 (21)	307 (23)	286 (20)	311 (21)	180 (16)	3563 (22)
Exposure category							
Sex between males	5042 (53)	884 (55)	794 (59)	922 (64)	953 (64)	870 (75)	9465 (57)
Injection drug use	2482 (26)	226 (14)	149 (11)	98 (7)	64 (4)	28 (2)	3047 (18)
Sex between males-females	1976 (21)	505 (31)	395 (30)	426 (29)	463 (31)	257 (22)	4022 (24)
Age at seroconversion, y							
15-24	2953 (31)	322 (20)	233 (17)	257 (18)	237 (16)	171 (15)	4173 (25)
25-34	4505 (47)	780 (48)	658 (49)	643 (44)	637 (43)	494 (43)	7717 (47)
35-44	1480 (16)	352 (22)	304 (23)	360 (25)	415 (28)	343 (30)	3254 (20)
$\geq$ 45	562 (6)	161 (10)	143 (11)	186 (13)	191 (13)	147 (13)	1390 (8)
Median (IQR)	27 (23-33)	30 (26-37)	31 (26-37)	32 (26-38)	33 (27-39)	33 (27-39)	29 (24-36)

Abbreviation: IQR, interquartile range.

**Table 2.** Changes in Overall and Excess Mortality Rates

Mortality	Calendar Period						Total
	Pre-1996	1996-1997	1998-1999	2000-2001	2002-2003	2004-2006	
Person-years of follow-up	31 302	14 434	16 656	18 205	17 323	14 703	112 624
Observed deaths	1332	481	231	212	188	127	2571
Expected deaths <sup>a</sup>	56.1	28.4	33.2	38.9	40.9	37.4	234.8
Excess deaths (95% CI)	1275.9 (1205.9-1345.9)	452.6 (410.9-494.3)	197.8 (170.2-225.3)	173.1 (147.4-198.9)	147.1 (123.4-170.9)	89.6 (71.0-108.1)	2336.2 (2241.4-2430.9)
Overall mortality rate (95% CI), per 1000 person-years <sup>b</sup>	42.6 (40.3-44.8)	33.3 (30.3-36.3)	13.9 (12.1-15.7)	11.6 (10.1-13.2)	10.9 (9.3-12.4)	8.6 (7.1-10.1)	22.8 (21.9-23.7)
Excess mortality rate (95% CI), per 1000 person-years <sup>c</sup>	40.8 (38.5-43.0)	31.4 (28.5-34.2)	11.9 (10.2-13.5)	9.5 (8.1-10.9)	8.5 (7.1-9.9)	6.1 (4.8-7.4)	20.7 (19.9-21.6)

Abbreviation: CI, confidence interval.

<sup>a</sup> Estimated by applying general population mortality rates to a hypothetical cohort matched to the study population on age, sex, calendar year at risk, and country.

<sup>b</sup> Calculated as  $1000 \times (\text{observed deaths})/(\text{person-years of follow-up})$ .

<sup>c</sup> Calculated as  $1000 \times (\text{excess deaths})/(\text{person-years of follow-up})$ .

(TABLE 3). There was no overall effect of exposure category in the pre-1996 period ( $P = .29$ ). In each subsequent calendar period, exposure category was strongly predictive of excess mortality ( $P < .001$  in each period), with those exposed through IDU at significantly higher risk than those exposed through sex between males (eHR, 3.71; 95% CI, 2.05-6.73 in 2004-2006). Those exposed via sex between males and females had a risk of excess mortality similar to that of those exposed via sex between males in every period except 2000-2001, when they were at higher risk (eHR, 2.02; 95% CI, 1.18-3.45).

For age at seroconversion and sex there was no evidence of variation over calendar time in the final model ( $P = .40$  and  $P = .45$ , respectively, for interaction). Over all calendar periods there was a clear gradient of increasing risk of excess mortality with increasing age at seroconversion. Females were at consistently lower risk than males.

All estimates were very similar in 2 sensitivity analyses in which time since seroconversion was split into smaller intervals (3 and 6 months) for the first 2 years of infection.

### Estimated Excess Mortality by Duration of Infection

Considering those in the sexual HIV exposure groups, mortality among HIV-infected individuals decreased toward background mortality levels between pre-1996 and 2004-2006 (FIGURE). Because individuals in the IDU exposure category are likely to be at higher risk of mortality than the general population regardless of HIV infection, this category was initially excluded from estimates of the cumulative excess mortality. Comparing the cumulative overall and excess probability of death, we found that prior to 1996, excess mortality above that expected in the general population accounted for the vast majority of total observed mortality in CASCADE in all age groups and at all stages of infection (TABLE 4). However, excess mortality decreased dramatically from 1996 onward. By 2004-2006, there was no evidence of any excess mortality to 5 years from seroconversion in any age group. However, in the longer term, some excess mortality was still evident, with the cumulative excess probability of death in the first 10 years from seroconversion

estimated to be 4.8% (95% CI, 2.5%-8.6%) in those aged 15 to 24 years and 4.3% (95% CI, 0.0%-10.5%) in those 45 years or older at seroconversion, though in the latter age group this excess mortality represented less than half of the total 10-year mortality of 12.2%.

Among individuals exposed through IDU, in contrast, mortality in 2004-2006 was higher than background levels, even early in infection (estimated cumulative excess probability of death in the first 5 and 10 years, 4.8% [95% CI, 1.4%-13.6%] and 6.2% [95% CI, 2.2%-14.3%], respectively, among those exposed through IDU who were younger than 45 years at seroconversion).

To further explore the differences between HIV exposure groups, we considered causes of death in 2004-2006. Of the 127 individuals who died in this period, 95 had known cause of death (as recorded in clinic records or death certificates), the most common being AIDS for 27 individuals (28%), non-AIDS malignancy for 14 (15%), and suicide or intentional harm for 13 (14%). The pattern of causes of death among those exposed through IDU differed from that of other groups: no non-AIDS malig-

**Table 3.** Excess Hazard Ratios (eHRs) Obtained Using a Multivariate Model for Excess Mortality<sup>a</sup>

	eHR (95% CI) by Calendar Period						P Value <sup>b</sup>
	Pre-1996	1996-1997	1998-1999	2000-2001	2002-2003	2004-2006	
No. of deaths	1332	481	231	212	188	127	
Calendar period <sup>c</sup>	1 [Reference]	0.51 (0.39-0.67)	0.12 (0.08-0.18)	0.05 (0.03-0.09)	0.07 (0.04-0.11)	0.05 (0.03-0.09)	
Age at seroconversion, y							
15-24	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	.40
25-34	1.54 (1.34-1.78)	1.13 (0.90-1.42)	1.07 (0.75-1.52)	1.37 (0.94-2.00)	1.03 (0.68-1.55)	1.08 (0.62-1.91)	
35-44	2.05 (1.71-2.45)	1.67 (1.23-2.27)	1.85 (1.15-2.98)	2.42 (1.46-4.02)	1.59 (0.91-2.79)	1.38 (0.64-2.98)	
≥45	2.37 (1.84-3.06)	2.81 (1.90-4.16)	2.81 (1.40-5.61)	2.62 (1.12-6.13)	1.94 (0.75-5.02)	2.71 (1.03-7.11)	
P value <sup>d</sup>	< .001	< .001	.003	.004	.21	.20	
Exposure category							
Sex between males	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	< .001
Injection drug use	0.99 (0.86-1.14)	1.65 (1.30-2.09)	3.46 (2.39-5.02)	5.21 (3.38-8.04)	4.77 (3.06-7.44)	3.71 (2.05-6.73)	
Sex between males-females	0.85 (0.68-1.05)	0.79 (0.56-1.11)	1.53 (0.92-2.53)	2.02 (1.18-3.45)	1.61 (0.90-2.89)	1.56 (0.74-3.29)	
P value <sup>d</sup>	.29	< .001	< .001	< .001	< .001	< .001	
Sex							
Male	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	.45
Female	0.76 (0.63-0.93)	0.95 (0.72-1.25)	0.55 (0.36-0.84)	0.83 (0.56-1.23)	0.74 (0.47-1.17)	0.75 (0.40-1.41)	
P value <sup>d</sup>	.006	.72	.006	.35	.20	.37	

Abbreviation: CI, confidence interval.

<sup>a</sup>Results are from multivariate relative survival model adjusted for all main effects and all interactions with calendar period. All  $P$  values calculated from likelihood ratio tests of nested models.

<sup>b</sup>For variation of effect between calendar periods.

<sup>c</sup>Calendar period effect estimates apply to the reference groups of age at seroconversion (15-24 y), sex (male), and exposure category (sex between males).

<sup>d</sup>For variation of effect within calendar period.

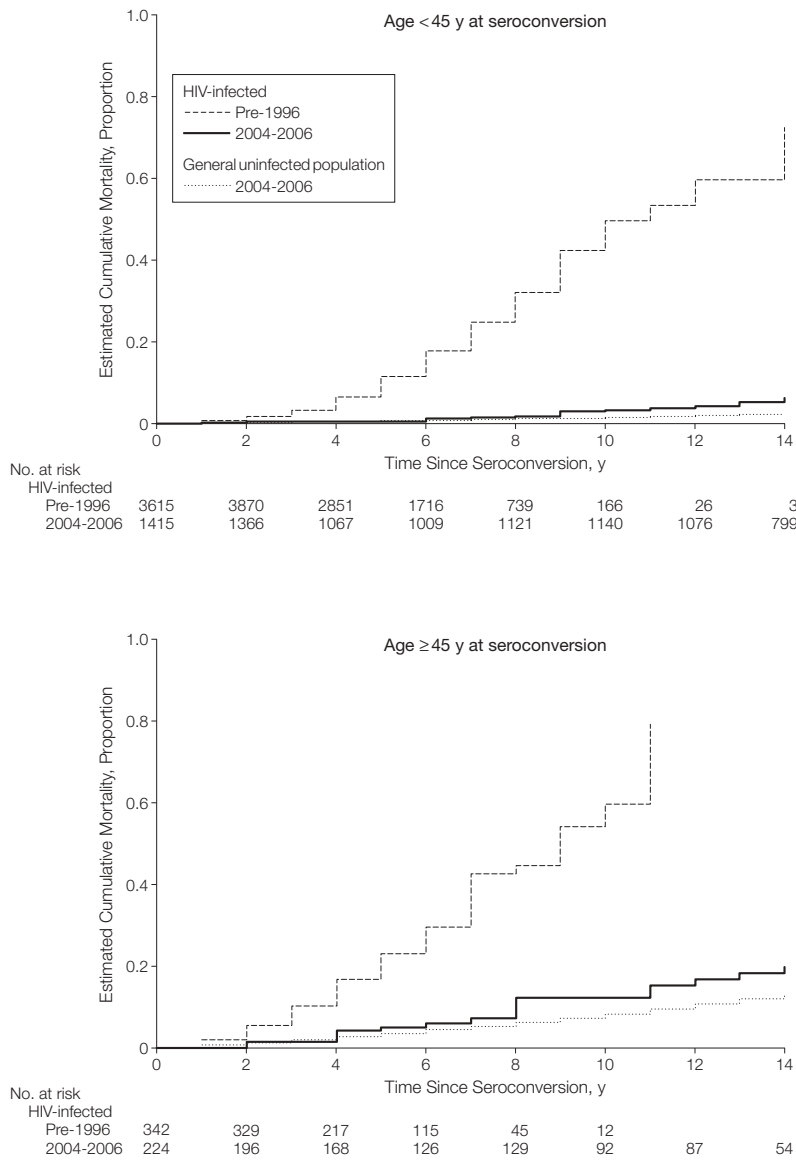
nancies were reported, and there was a higher proportion of reported liver-related causes (7/22 [32%], compared with 2/73 [3%] among sexual exposure groups). The proportion of deaths reported as suicide among those exposed through IDU was only slightly higher than among those with reported exposure category of sex between males (4/22 [18%] vs 8/51 [16%]).

**Uptake of HAART**

The median time from HIV seroconversion to starting HAART was 1.6 (IQR, 0.7-3.5) years in 1996-1997 and 1.4 (IQR, 0.6-3.4), 1.8 (IQR, 0.7-5.6), 2.4 (IQR, 0.8-6.7), and 2.2 (IQR, 1.0-4.8) years in 1998-1999, 2000-2001, 2002-2003, and 2004-2006, respectively. After excluding time at risk when HAART would not be indicated,

the proportion of person-time spent receiving HAART increased from 17% in 1996-1997 to 54%, 66%, 69%, and 73% in the same calendar periods, respectively. As expected, the use of nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens increased over time and by 2004-2006, the proportion of person-time receiving NNRTI-based HAART was approximately equal to that spent receiving protease inhibitor (PI)-based HAART (40% and 42% of person-time on HAART, respectively, compared with 18% and 71%, respectively, in 1998-1999, when the first NNRTIs were available). Ritonavir boosting of PI regimens also increased from 7.0% of person-time receiving PI-based HAART in 1996-1997 to 10.7%, 32%, 63%, and 79% in 1998-1999, 2000-2001, 2002-2003, and 2004-2006, respectively.

**Figure.** Reduction in All-Cause Mortality pre-1996 to 2006 and Comparison With That of the General Population, by Age Group



The general population curve for 2004-2006 was generated by applying general population mortality rates in each 1-year interval since seroconversion to a hypothetical cohort matched to the study population on age, sex, and country. HIV indicates human immunodeficiency virus.

**COMMENT**

We found that the gap in mortality rates between HIV-infected individuals in our study and the general population narrowed in every calendar period from 1996 onward. Considering the first years following the widespread introduction of HAART, we have estimated an 88% reduction in excess mortality in 2000-2001 compared with pre-1996, corresponding closely to the 87% reduction in the standardized mortality ratio in 1997-2001 compared with pre-1996, as reported by the Swiss HIV cohort.<sup>7</sup> Our more recent data show that reductions have continued to 2004-2006, with excess mortality in this period 94% lower than pre-1996 levels. Corresponding to these reductions, the uptake of HAART increased, and though this leveled off after 2001, there followed an increasing use of NNRTI-based HAART as the first-line treatment regimen and a substantial increase in the boosting of PI-based regimens.

Despite the major reductions in excess mortality, a significantly increased risk of death remained among individuals of all ages in 2004-2006. A number of other studies comparing mortality in HIV-infected and uninfected populations have also found a

significant remaining excess mortality,<sup>10</sup> though we found a relatively low level of excess mortality among those 45 years or older compared with 1 study<sup>8</sup>; however, since that study considered time-updated acquired age rather than age at HIV seroconversion, it is likely that those contributing to the 45 years or older age groups

**Table 4.** Estimated Cumulative Overall Probability of Death by Duration of HIV Infection Among Sexual Exposure Groups in CASCADE and Cumulative Excess Probability of Death Compared With That of the General Population<sup>a</sup>

Age at/Time Since Seroconversion	Calendar Period					
	Pre-1996	1996-1997	1998-1999	2000-2001	2002-2003	2004-2006
15-24 y						
5 y						
Overall probability, %	8.3	4.9	2.9	0.8	1.3	0
Excess probability, % (95% CI)	7.9 (6.3 to 9.8)	4.5 (2.9 to 6.8)	2.5 (1.3 to 4.6)	0.4 (-0.1 to 2.0)	0.9 (0.1 to 3.3)	
10 y						
Overall probability, %	42.2	21.0	7.4	4.5	4.7	5.4
Excess probability, % (95% CI)	41.5 (35.5 to 48.1)	20.2 (16.6 to 24.3)	6.5 (4.4 to 9.4)	3.7 (2.2 to 6.1)	3.9 (2.1 to 6.8)	4.8 (2.5 to 8.6)
15 y						
Overall probability, %	NA <sup>b</sup>	37.2	12.5	8.8	11.4	8.1
Excess probability, % (95% CI)	NA <sup>b</sup>	36.2 (27.9 to 45.9)	11.2 (7.4 to 16.4)	7.6 (4.9 to 11.3)	10.2 (7.3 to 14.0)	7.0 (4.2 to 11.2)
25-34 y						
5 y						
Overall probability, %	11.1	5.0	2.0	1	0.4	0.3
Excess probability, % (95% CI)	10.5 (9.0 to 12.2)	4.4 (3.2 to 5.9)	1.4 (0.7 to 2.5)	0.4 (-0.1 to 1.4)	-0.1 (-0.4 to 0.6)	-0.2 (-0.4 to 0.7)
10 y						
Overall probability, %	48.3	21.1	5.9	5.3	2.7	2.0
Excess probability, % (95% CI)	47.5 (43.3 to 51.8)	19.9 (17.0 to 23.2)	4.7 (3.2 to 6.5)	4.1 (2.8 to 5.8)	1.5 (0.6 to 2.9)	0.9 (0.0 to 2.4)
15 y						
Overall probability, %	NA <sup>b</sup>	35.6	12.3	10.8	6.3	7.5
Excess probability, % (95% CI)	NA <sup>b</sup>	34.0 (24.8 to 45.1)	10.2 (6.8 to 14.7)	8.7 (6.2 to 11.9)	4.1 (2.5 to 6.3)	5.5 (3.5 to 8.1)
35-44 y						
5 y						
Overall probability, %	16.0	8.2	3.3	1.2	1.6	0.8
Excess probability, % (95% CI)	14.9 (12.4 to 17.9)	7.1 (4.7 to 10.4)	2.3 (0.9 to 4.5)	0.1 (-0.6 to 1.8)	0.5 (-0.3 to 2.3)	-0.2 (-0.7 to 1.0)
10 y						
Overall probability, %	61.4	28.9	10.3	4.5	7.2	3.7
Excess probability, % (95% CI)	60.3 (54.2 to 66.4)	26.7 (21.7 to 32.5)	7.8 (4.9 to 11.7)	1.9 (0.1 to 4.7)	4.7 (2.5 to 7.9)	1.3 (-0.3 to 4.0)
15 y						
Overall probability, %	68.2	67.1	29.1	13.3	14.0	7.2
Excess probability, % (95% CI)	66.5 (58.6 to 74.2)	65.3 (40.8 to 87.5)	25.3 (16.5 to 36.5)	8.6 (4.2 to 14.9)	9.4 (5.7 to 14.2)	2.4 (-0.4 to 6.8)
≥45 y						
5 y						
Overall probability, %	23.0	16.2	11.8	3.4	8.9	4.9
Excess probability, % (95% CI)	19.8 (15.3 to 25.3)	13.0 (8.3 to 19.1)	8.4 (4.5 to 13.7)	-0.3 (-2.1 to 3.4)	5.4 (2.0 to 10.4)	1.5 (-0.8 to 5.6)
10 y						
Overall probability, %	59.6	52.1	22.2	15.4	16.3	12.2
Excess probability, % (95% CI)	55.8 (45.2 to 66.5)	47.4 (37.3 to 58.2)	14.6 (8.5 to 22.2)	7.5 (2.3 to 14.6)	8.4 (3.2 to 15.6)	4.3 (0.0 to 10.5)
15 y						
Overall probability, %	NA <sup>b</sup>	NA <sup>b</sup>	28.6	23.4	25.3	24.9
Excess probability, % (95% CI)	NA <sup>b</sup>	NA <sup>b</sup>	16.1 (6.6 to 28.5)	9.7 (1.0 to 21.4)	11.5 (3.3 to 22.2)	11.9 (3.4 to 23.1)

Abbreviations: CASCADE; Concerted Action on Seroconversion to AIDS and Death in Europe; CI, confidence interval.

<sup>a</sup>Estimates are calculated as 100 minus the life-table based % cumulative survival and relative survival probabilities.

<sup>b</sup>NA indicates not applicable because of insufficient individuals remaining alive and at risk to calculate estimates.

had longer duration of infection, which was unknown in that study.

To our knowledge, no study to date has made a comparison of mortality among HIV-infected and uninfected individuals adjusted for duration of HIV infection, and our results provide estimates, hitherto unavailable, of the cumulative excess probability of death as duration of HIV infection increases. Interestingly, we found that by 2004-2006, the risk of death in the first 5 years following seroconversion was similar to that of the general population, with the excess probability of death becoming apparent only later in the course of infection. Our long-term cumulative mortality estimates for 2004-2006 include data from individuals infected in the mid-1990s or earlier who may have started antiretroviral treatment later in the course of infection and with regimens inferior to those currently available; thus, such estimates may be pessimistic in terms of the long-term outlook for more recently infected individuals. Nevertheless, it is likely that even with current standards of HIV management, some long-term excess mortality would remain because problems of toxicity, resistance, and therapy adherence are likely to increase with time receiving HAART.

We found that older age was highly predictive of excess mortality prior to 1996, and this effect broadly continued in later calendar periods, despite suggestions in the literature that increasing age is associated with better adherence to HAART.<sup>22</sup> Another large study<sup>23</sup> found an association between older age and overall mortality following HAART initiation. It is of interest that the effect persisted in our analysis adjusted for natural aging, which appeared to account for more than half of the total mortality in individuals 45 years or older in 2004-2006. Some studies have found that older individuals experience slower immune recovery following HAART initiation,<sup>24,25</sup> which could reflect the state of thymic function and may in part account for their continuing excess risk of death.<sup>26</sup>

Individuals exposed through IDU had a higher excess risk of death throughout the HAART era, with a 4-fold higher risk compared with the reported exposure category of sex between males in 2004-2006. It is unlikely that HIV infection is the only factor leading to increased mortality rates among those exposed through IDU, who, as well as accounting for the direct risks of substance abuse, may be more likely to be diagnosed with mental health-related illnesses<sup>27</sup> and coinfections,<sup>28</sup> the effects of which may have been masked prior to 1997 by the mortality burden of HIV disease itself. On the other hand, the increasing separation of those exposed through IDU since 1997 as a group with higher excess mortality may point to differences in access and adherence to therapy. Indeed, we found a lower uptake of HAART among those exposed through IDU compared with other groups, while lower therapy adherence among such individuals has been described in the literature.<sup>29</sup>

Our study has some limitations. Ideally we would like to quantify the excess mortality associated with HIV infection. To this end, we have compared mortality in CASCADE with that in the general population. Although we matched by age, sex, calendar time, and country, it is likely that HIV-infected individuals in our study differ from the general population in other ways. Rates of smoking have been shown to be high among some HIV-infected populations<sup>30</sup>; other risk behaviors, socioeconomic factors, and race/ethnicity are also likely to differ among HIV-infected persons. Those exposed through IDU in particular are likely to be at higher risk of mortality than the general population regardless of HIV infection, and we have presented our estimates of the cumulative excess mortality proportion excluding this group. Nonetheless, our results are interpretable as estimates of the excess mortality among HIV-infected individuals, who may differ from a general population not only in being infected with HIV but also in other factors.

A second limitation is that HIV seroconverters are not representative of the total HIV-infected population; mortality estimates derived from seroconverters, by definition diagnosed and monitored from an early stage, are likely to be optimistic compared with the experience of the wider HIV-infected population. In particular, further research will be needed before our finding of no excess mortality in the first 5 years of infection in 2004-2006 can be generalized beyond those diagnosed early in infection.

Despite these limitations, seroconverters provide a unique opportunity to study and adjust for the effect of duration of HIV infection on mortality and excess mortality. Our results show the progress in reducing mortality among HIV-infected individuals toward the levels experienced by the general uninfected population. However, there is continuing excess mortality, particularly evident in those infected for 10 years or more. Ongoing monitoring of excess mortality will be important as new treatment advances are implemented in an attempt to further reduce mortality rates among HIV-infected individuals.

**Author Contributions:** Mr Bhaskaran had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Bhaskaran, Johnson, Porter.  
**Acquisition of data:** Bhaskaran, Hamouda, Sannes, Boufassa.

**Analysis and interpretation of data:** Bhaskaran, Lambert, Porter.

**Drafting of the manuscript:** Bhaskaran, Sannes, Porter.  
**Critical revision of the manuscript for important intellectual content:** Hamouda, Boufassa, Johnson, Lambert, Porter.

**Statistical analysis:** Bhaskaran, Lambert.

**Obtained funding:** Porter.

**Administrative, technical, or material support:** Hamouda, Sannes, Boufassa, Porter.

**Study supervision:** Bhaskaran, Johnson, Porter.

**Financial Disclosures:** None reported.

**Funding/Support:** The CASCADE collaboration has been funded through grants BMH4-CT97-2550, QLK2-2000-01431, QLRT-2001-01708, and LSHP-CT-2006-018949 from the European Union.

**Role of the Sponsor:** The European Union had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

**CASCADE Collaboration Steering Committee:** Julia Del Amo, MD, Instituto de Salud Carlos III, Madrid, Spain (Chair); Laurence Meyer, MD, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France (Vice Chair); Heiner Bucher, MD, Hospices Can-

tonaux Centre Hospitalier Universitaire Vaudois (CHUV), Basel, Switzerland; Geneviève Chêne, MD, Université Bordeaux 2, Bordeaux, France; Deenan Pillay, MD, University College London (UCL), London, United Kingdom; Maria Prins, PhD, Municipal Health Service, Amsterdam, the Netherlands; Magda Rosinska, MD, National Institute of Hygiene, Warsaw, Poland; Caroline Sabin, PhD, UCL, London, United Kingdom; Giota Touloumi, PhD, National and Kapodistrian University of Athens, Athens, Greece. **Coordinating Center:** Kholoud Porter, PhD (Project Leader), Krishnan Bhaskaran, MSc (Scientific Coordinator), Sarah Walker, PhD, Abdel Babiker, PhD, Janet Darbyshire, MD, Medical Research Council Clinical Trials Unit (MRC CTU), London, United Kingdom. **Clinical Advisory Board:** Heiner Bucher, MD, Hospices Cantonaux CHUV, Basel, Switzerland; Andrea de Luca, MD, Catholic University, Rome, Italy; Martin Fisher, Brighton Hospitals Healthcare Trust, Brighton, United Kingdom; Roberto Muga, MD, Hospital Universitari Germans Trias i Pujol, Badalona, Spain. **Collaborators:** **Australia:** Sydney AIDS Prospective Study and Sydney Primary HIV Infection cohort (John Kaldor, PhD, Tony Kelleher, PhD, Tim Ramacciotti, Linda Gelgor, David Cooper, MD, Don Smith, MD, National Centre in HIV Epidemiology and Clinical Research, Sydney). **Canada:** Southern Alberta Clinic (John Gill, MD, Calgary). **Denmark:** Copenhagen HIV Seroconverter Cohort (Louise Bruun Jørgensen, PhD, Claus Nielsen, MD, Statens Serum Institute, Copenhagen; Court Pedersen MD, Odense University Hospital, Odense). **Estonia:** Tartu

Ülikool (Irja Lutsar, MD, Tartu). **France:** Aquitaine cohort (Geneviève Chêne, MD, Francois Dabis, MD, Rodolphe Thiebaut, MD, Bernard Masquelier, PhD, Université Bordeaux 2, Bordeaux), French Hospital Database (Dominique Costagliola, PhD, Marguerite Guiguet, PhD, INSERM, Paris), Lyon Primary Infection cohort (Philippe Vanhems, MD, Université Claude Bernard Lyon 1, Lyon), SEROCO cohort (Laurence Meyer, MD, Farouly Boufassa, MD, INSERM, Paris). **Germany:** German cohort (Osamah Hamouda, MD, Claudia Kuchner, MD, Robert Koch Institute, Berlin). **Greece:** Greek Haemophilia cohort (Giota Touloumi, PhD, Nikos Pantazis, PhD, Angelos Hatzakis, MD, Dimitrios Paraskevis, PhD, National and Kapodistrian University of Athens; Anastasia Karafoulidou, MD, Laikon General Hospital, Athens). **Italy:** Italian Seroconversion Study (Giovanni Rezza, MD, Maria Dorrucchi, PhD, Benedetta Longo, MD, Istituto Superiore di Sanità, Rome; Claudia Balotta, PhD, Università degli Studi di Milano, Milan). **The Netherlands:** Amsterdam Cohort Studies among homosexual men and drug users (Maria Prins, PhD, Liselotte van Asten, PhD, Akke van der Bij, PhD, Ronald Geskus, PhD, Roel Coutinho, MD, Municipal Health Service, Amsterdam). **Norway:** Oslo and Ullevål Hospital cohorts (Mette Sannes, Oddbjorn Brubakk, MD, Anne Eskild, MD, Johan N. Bruun, MD, Ullevål University Hospital, Oslo). **Poland:** National Institute of Hygiene, Warsaw (Magdalena Rosinska, MD). **Portugal:** Universidade Nova de Lisboa, Lisbon (Ricardo Camacho, MD). **Russia:** Pasteur Institute, St Petersburg

(Tatyana Smolskaya, MD). **Spain:** Badalona IDU hospital cohort (Roberto Muga, MD, Hospital Universitari Germans Trias i Pujol, Badalona), Barcelona IDU Cohort (Patricia Garcia de Olalla, MD, Agency of Public Health of Barcelona, Barcelona), Madrid cohort (Julia Del Amo, MD, Instituto de Salud Carlos III, Madrid, Jorge del Romero, MD, Sandoval clinic, Madrid), Valencia IDU cohort (Santiago Pérez-Hoyos, PhD, Ildefonso Hernandez Aguado, MD, Universidad Miguel Hernandez, Alicante). **Switzerland:** Swiss HIV cohort (Heiner Bucher, MD, Martin Rickenbach, MD, Patrick Francioli, MD, Hospices Cantonaux CHUV, Lausanne, Switzerland). **Ukraine:** Perinatal Prevention of AIDS Initiative, Odessa (Ruslan Malyuta, MD). **United Kingdom:** Edinburgh Hospital cohort (Ray Brettler, MD, Western General Hospital, Edinburgh), Health Protection Agency (HPA), London (Valerie Delpech, MD, Sam Lattimore, PhD, Gary Murphy, PhD, John Parry, PhD, Noel Gill, MD), Royal Free haemophilia cohort (Caroline Sabin, PhD, UCLMS, London; Christine Lee, MD, Royal Free Hospital Trust, London), UK Register of HIV Seroconverters (Kholoud Porter, PhD, MRC CTU, London; Anne Johnson, MD, UCLMS, London; Andrew Phillips, PhD, UCLMS, London; Abdel Babiker, PhD, MRC CTU, London; Janet Darbyshire, MD, MRC CTU, London; Valerie Delpech, MD, HPA, London), University College London, London (Deenan Pillay, MD), University of Oxford, Oxford (Harold Jaffe, MD). **Previous Presentation:** Presented in part at the 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, Massachusetts.

## REFERENCES

- Porter K, Babiker A, Bhaskaran K, et al; CASCADE Collaboration. Determinants of survival following HIV-1 seroconversion after the introduction of HAART. *Lancet*. 2003;362(9392):1267-1274.
- Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*. 2003;362(9377):22-29.
- Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. *Natl Cancer Inst Monogr*. 1961;6:101-121.
- Roy P, Vaughan Hudson G, Vaughan Hudson B, Esteve J, Swerdlow AJ. Long-term survival in Hodgkin's disease patients: a comparison of relative survival in patients in trials and those recorded in population-based cancer registries. *Eur J Cancer*. 2000;36(3):384-389.
- Colonna M, Grande E, Jonasson JG; Eurocare Working Group. Variation in relative survival of thyroid cancers in Europe: results from the analysis on 21 countries over the period 1983-1994 (EURO-CARE-3 study). *Eur J Cancer*. 2006;42(15):2598-2608.
- Capocaccia R, Gatta G, Roazzi P, et al. The EURO-CARE-3 database: methodology of data collection, standardisation, quality control and statistical analysis. *Ann Oncol*. 2003;14(suppl 5):v14-v27.
- Keiser O, Taffe P, Zwahlen M, et al. All cause mortality in the Swiss HIV Cohort Study from 1990 to 2001 in comparison with the Swiss population. *AIDS*. 2004;18(13):1835-1843.
- Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. *Ann Intern Med*. 2007;146(2):87-95.
- Jaggy C, von Overbeck J, Ledergerber B, et al. Mortality in the Swiss HIV Cohort Study (SHCS) and the Swiss general population. *Lancet*. 2003;362(9387):877-878.
- van Sighem A, Danner S, Ghani AC, Gras L, Anderson RM, de Wolf F. Mortality in patients with successful initial response to highly active antiretroviral therapy is still higher than in non-HIV-infected individuals. *J Acquir Immune Defic Syndr*. 2005;40(2):212-218.
- CASCADE Collaboration. Effect of ignoring the time of HIV seroconversion in estimating changes in survival over calendar time in observational studies: results from CASCADE. *AIDS*. 2000;14(13):1899-1906.
- CASCADE Collaboration. Changes in the uptake of antiretroviral therapy and survival in people with known duration of HIV infection in Europe: results from CASCADE. *HIV Med*. 2000;1(4):224-231.
- Ewings FM, Bhaskaran K, McLean K, et al. Survival following HIV infection of a cohort followed up from seroconversion in the UK. *AIDS*. 2008;22(1):89-95.
- Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81(3):515-526.
- Ederer F, Heise H. Instructions to IBM650 programmers in processing survival computations. Bethesda, MD: End Results Evaluation Section, National Cancer Institute; 1959. Methodological note No. 10.
- Human Mortality Database. Human Mortality Database Web site. <http://www.mortality.org>. 2007. Accessed July 2007.
- Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med*. 2004;23(1):51-64.
- Cutler SJ, Ederer F. Maximum utilisation of the life table method in analyzing survival. *J Chronic Dis*. 1958;8(6):699-712.
- Brenner H, Hakulinen T. Long-term cancer patient survival achieved by the end of the 20th century: most up-to-date estimates from the nationwide Finnish cancer registry. *Br J Cancer*. 2001;85(3):367-371.
- Gazzard B, Bernard AJ, Boffito M, et al. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006). *HIV Med*. 2006;7(8):487-503.
- Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. *JAMA*. 2006;296(7):827-843.
- Silverberg MJ, Leyden W, Horberg MA, DeLorenzo GN, Klein D, Quisenberry CP Jr. Older age and the response to and tolerability of antiretroviral therapy. *Arch Intern Med*. 2007;167(7):684-691.
- May M, Sterne JA, Sabin C, et al; Antiretroviral Therapy (ART) Cohort Collaboration. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. *AIDS*. 2007;21(9):1185-1197.
- Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. *Arch Intern Med*. 2003;163(18):2187-2195.
- Viard JP, Mocroft A, Chiesi A, et al. Influence of age on CD4 cell recovery in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study. *J Infect Dis*. 2001;183(8):1290-1294.
- Hinkin CH, Hardy DJ, Mason KI, et al. Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *AIDS*. 2004;18(suppl 1):S19-S25.
- Chander H, Himelhoch S, Moore RD. Substance abuse and psychiatric disorders in HIV-positive patients: epidemiology and impact on antiretroviral therapy. *Drugs*. 2006;66(6):769-789.
- Rockstroh JK, Mocroft A, Soriano V, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. *J Infect Dis*. 2005;192(6):992-1002.
- Lert F, Kazatchkine MD. Antiretroviral HIV treatment and care for injecting drug users: an evidence-based overview. *Int J Drug Policy*. 2007;18(4):255-261.
- Friis-Møller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients—association with antiretroviral therapy: results from the DAD study. *AIDS*. 2003;17(8):1179-1193.