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Excess mortality in patients with AIDS in the era of highly active antiretroviral therapy: Temporal changes and risk factors

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Abstract

Background—Excess mortality has declined among HIV infected patients but without evidence of a decline in patients with AIDS. We assessed temporal changes in excess mortality and elucidated risk factors for excess mortality in patients with AIDS diagnosed in the era of highly active antiretroviral therapy (HAART).

Methods—We included 1,188 patients of the Longitudinal Study of Ocular Complications in AIDS who were between 25-64 years old at enrollment and diagnosed with AIDS after 1995. We calculated excess mortality as the age-, year- and sex-adjusted difference in mortality rates between patients with AIDS and persons in the US general population, between 1999 and 2007, and used a relative survival model to identify risk factors for excess mortality.

Results—There were an average of 50 excess deaths (95% CI 44-57) per 1,000 person years between 1999 and 2007. Excess mortality almost halved with an annual decline of 8.0% per year (3.0-12.7 p=0.002) but remained high at 36 excess deaths per 1,000 person years in 2007. Viral load >400 vs. ≤400 copies/mL (risk ratio 3.4 [2.3-5.0]), CD4+ count <200 vs. ≥200 cells/μL (2.7 [1.9-3.9]) and cytomegalovirus retinitis (1.6 [1.2-2.1]) were the strongest risk factors for excess mortality.

Conclusions—Excess mortality among patients with AIDS was nearly halved in the HAART era and most strongly linked to stage of HIV disease. These results reflect the continuing improvements in AIDS management but also highlight that excess mortality remains about five times higher in patients with AIDS than in patients with HIV-infection but no AIDS.

Keywords

AIDS; mortality; Highly Active Antiretroviral Therapy; Cohort Studies

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Introduction

A recent analysis from the CASCADE HIV cohorts (Concerted Action on Seroconversion to AIDS and Death in Europe) reported that excess mortality among HIV-infected persons has decreased dramatically since the introduction of highly active antiretroviral therapy (HAART).(1) Excess mortality, defined as deaths occurring in excess of the rate observed in the general population, declined from 41 per 1,000 person years in the pre-HAART era to only 6 per 1,000 person years in the years 2004 to 2006. The continued reduction in excess mortality paralleled the uptake of HAART as first line treatment.

Comparing mortality rates among HIV-infected patients to rates in the general population provides a natural reference point that indicates the impact of HIV infection upon survival at a population level and is an index of the effectiveness of antiretroviral treatment.(1-7) In addition, such comparisons may offer insights into factors that could explain the observed variability in excess mortality rates encountered among HIV-infected patients. Accounting for such variability can help formulate strategies on how to optimize HIV care.

Although HAART use has dramatically decreased death rates among persons with AIDS(6) it is unknown to what extent HAART-related decreases in excess mortality observed among HIV-infected persons exist among patients with AIDS. .. Also, although the recent analysis of the CASCADE cohorts was based on a large number of patients, covariates evaluated to assess the risks for excess mortality included age at seroconversion, sex and HIV exposure category only. Other, potentially more important correlates of mortality such as CD4+ T-cell count, cytomegalovirus (CMV) retinitis or quantitative plasma HIV RNA level (viral load) have not been explored. The Longitudinal Study of Ocular Complications in AIDS (LSOCA), funded by the National Eye Institute, is one of a few cohort studies limited to persons diagnosed with AIDS but without further exclusions.(8, 9) Our aims here are to assess the extent of decline in excess mortality over time and, to elucidate risk factors for excess mortality among patients participating in LSOCA who have been diagnosed with AIDS in the HAART era compared to persons in the general United States population.

Methods

LSOCA is a prospective observational study of patients with AIDS, who were at least 13 years of age at enrollment.(8, 9) Enrollees have AIDS diagnosed according to the 1993 Centers for Disease Control and Prevention case surveillance definition of AIDS. Patients with incident and prevalent AIDS are included. Since September 1998, recruitment has been performed at 19 clinical centers across the United States, located in urban areas with sizable HIV-infected populations. The study protocol was reviewed and approved by institutional review boards at each of the participating clinics and the coordinating center. The study is conducted in accordance with the principles of the Declaration of Helsinki. Adult patients have given written informed consent. For adolescents, a Consent Statement has been signed by parents or guardians and an Assent Statement signed by adolescents and their parents or guardians.

At enrollment, all participants provide a medical history, including information on AIDS-related illnesses and antiretroviral therapy, and undergo an ophthalmologic examination. Laboratory tests performed at enrollment and follow-up include hematology, lymphocyte subset analysis, and, in patients with a major ocular complication, serum chemistry. More detailed information about the study protocol, data forms and the study handbook is available on www.lsoca.com.

In this analysis, we included patients enrolled between January 1999 and December 2007who were diagnosed with AIDS during the HAART era (from January 1996 onwards).

We did not consider the year 1998 in the analyses because recruitment had just started with too few patients enrolled (n=9) to provide a meaningful comparison to the death rates of the general population. We excluded the year 2008 from the analyses because of the yet incomplete reporting of final death data to the data coordination center. We also excluded patients younger than 25 (n=20) or older than 64 years of age (n=15) because a comparison of these age groups, that would need further stratification into calendar year and sex, against mortality rates of the general US population would be too imprecise. We decided against merging patients in these age groups with other age groups because mortality rates can change substantially from one 5-year category to the next (for example, 1,596 deaths per 100,000 persons for 60-64 year old males in 1999 versus 2479 in the 65-70 year old males).

Statistical analysis

The primary aim of the analysis was to assess declines in excess mortality in patients with AIDS enrolled in the LSOCA cohort. In an additional analysis, we assessed patient characteristics associated with excess mortality.

We defined excess mortality as the age-, year- and sex-adjusted difference in mortality rates between patients with AIDS and persons in the US general population. In a first step we calculated mortality rates for patients enrolled in LSOCA for each calendar year (1999-2007) and compared them to mortality rates of the US population adjusting for calendar year, age and sex. We retrieved the mortality rates of the US population from the Vital Statistics report of the US Center for Disease Control and Prevention. (http://www.cdc.gov/nchs/nvss.htm) For the years 2006 and 2007, for which mortality rates have not yet been released we used multiple imputation ("ice" command of STATA) to generate age- and sex-stratified mortality rates for 2006 and 2007. We based the multiple imputation on age-adjusted death rates from the Vital Statistics reports 1999 to 2005 (for men and women separately) and used weights to indicate that the death rate estimates are based on a large number of observations. We generated 100 data sets and took the medians as an estimate of the age- and sex-stratified mortality rates for 2006 and 2007.

Based on these mortality rates we compared, for each year of follow-up, the observed mortality rates (in the LSOCA cohort) with the mortality rates of the general US population, adjusting for age and sex. We considered matched individuals from the US population to be at risk until the corresponding LSOCA patient died or was censored (Ederer II method (10, 11)). In order to quantify the average extent of decline in mortality rates per year, we used Poisson regression analysis with the number of excess deaths as the dependent variable and the calendar year as independent variable and reported the average annual decline in %. In addition, we extracted the number of excess deaths, observation time and excess mortality per 1,000 person years from the publication on excess mortality in the CASCADE cohort in order to compare (declines in) excess mortality observed among AIDS (LSOCA cohort) and overall HIV-infected patients (CASCADE cohorts).

We stratified the analysis for moderate to high and for low CD4+ count (≥ or < 200 cells/μL) at enrollment, which reflects the long-term prognosis based on CD4+ counts. We conducted a number of sensitivity analyses to further assess the association of CD4+ count status (≥ or < 200 cells/μL) and change of excess mortality over time. First, we repeated the analysis excluding the years 1999 and 2000 because of the low number of enrollees in these years. Second, we considered CD4+ counts of individual patients for each year of observation following enrollment (no time lag between CD4+ measurement and year of observation) because CD4+ counts vary within individuals over time (with and without HAART). This analysis reflects the immediate association between CD4+ counts and mortality. Third, we also considered 2- and 4-year lags between CD4+ measurements and year of observation. Finally, we also planned to stratify the analysis for nadir CD4+ count

before enrollment into LSOCA but the number of patients with nadir CD4+ count ≥200 cells/mm^3 was too low to provide a meaningful analysis.

To assess the association of potential risk factors with excess mortality we used a Poisson regression model while offsetting the expected deaths, which adjusts for the mortality observed in the general population (background mortality).(11, 12) The model provides estimates of excess risk ratios, where the interpretation is similar to that of the risk ratio. The risk factors included age, sex, race (white, black, other), type of HIV exposure (men having sex with men, injection drug use, other), CD4+ cell count at enrollment into LSOCA (categorized into CD4+ of <200, 200-499 and ≥500 cells/μL), nadir CD4+ cell count (categorized into CD4+ of <100 and ≥100 cells/μL), plasma HIV RNA (viral load) level at enrollment (categorized into<400 and ≥400 copies/mL), CMV retinitis, time since AIDS diagnosis and calendar year of enrollment. To include all eligible patients in the analyses, we assumed that viral load was above 400 (copies/mL) in the 64 patients (5.4%) with missing data at study enrollment. We had complete data for the other variables. All analyses were conducted using STATA (STATA™ for Windows, version 10.1, Stata Corp; College Station, TX).

Results

As of 31 December 2008, there were 2,221 patients enrolled into LSOCA. We included 1,188 patients in the present analysis who were diagnosed with AIDS in the HAART era and enrolled into LSOCA between January 1999 and December 2007. We excluded patients with a diagnosis of AIDS before 1996 (n=863), enrollment in 1998 (n=9) or in 2008 (n=90), patients with a missing date of AIDS diagnosis (n=36), patients below 25 (n=20) or above 64 (n=15) years of age.

Patients were predominantly male (76.2%), of non-hispanic white (38.9%) or black ethnicity (41.4%), and diagnosed with AIDS more than a year before enrollment into LSOCA (61.6%, Table 1). There was a wide distribution of CD4+ cell counts and HIV RNA (viral load) levels and 19.6% of patients had CMV retinitis. Overall, 81.6% of patients received HAART and the proportions of patients who received HAART did not change over time; this was true for both patients who died (70.0%) or were censored (85.4%) between 1999 and 2008.

Decline in excess mortality in AIDS patients from 1999 to 2007

There were 293 (24.7%) patients who died, with an average duration of follow-up of 4.67 years (SD 3.07). Over the entire study period, the mortality rate was 53.5 per 1,000 patient years (95% CI 47.7 to 60.0). The average excess mortality rate per year was 50.2 (95% CI 44.2 to 56.5) per 1000 person years. Excess mortality declined between 1999 and 2007 from approximately 70 excess deaths per 1,000 person years in 1999 through 2001 to approximately 40 excess deaths per 1,000 person years in 2006 and 2007 (Figure 1). Based on a Poisson regression model the average annual decline was 8.0% (95% CI 3.0 to 12.7 p=0.002), Excess mortality in the CASCADE HIV cohorts averaged 9.1 excess deaths per 1,000 person years between 1999 and 2005, the average annual decline in excess mortality in HIV patients enrolled in the CASCADE cohorts was 4.8% (95% CI 3.1 to 6.5, p<0.001).

For patients with low CD4+ cell count (<200 cells/ μL) the average excess mortality rate per year was 74.0 (95% CI 64.5-84.4) per 1,000 person years and in patients with moderate to high CD4+ counts (≥200 cells/ μL) it was 21.1 (95% CI 15.5 to 28.1) per 1,000 person years (Figure 2). Excess mortality declined substantially in patients with low CD4+ cell count between 1999 and 2007 (8.3% per year [95% CI 2.7 to 13.4], p=0.004) whereas there was no decline in patients with moderate to high CD4+ cell counts (1.4% [95% CI -10.7 to 15.3],

p=0.83). The interaction between CD4+ count status and year was not statistically significant (p=0.16).

In the sensitivity analysis here we only considered the years 2001 to 2007, excess mortality declined by 11.4% per year (8.3% [95% CI 4.8 to 17.5], p=0.001) in patients with low CD4+ cell count whereas there was no decline in patients with moderate to high CD4+ counts (6.1% [95% CI -9.0 to 23.8], p=0.45). The interaction between CD4+ count status and year was marginally significant (p=0.034). In additional sensitivity analyses where we considered CD4+ count for each year of observation (no time lag between CD4+ measurement and year of observation) and a 2- and 4-year lag we did not find statistically significant interactions between CD4+ count status and year (p=0.24 for no time lag, p=0.68 for 2-year time lag and p=0.18 for 4-year time lag) either that would indicate statistically significantly different declines in excess mortality between patients with low and moderate to CD4+ count over time.

Risk factors for excess mortality in AIDS patients

A high plasma HIV RNA (viral load,>400 copies/mL), and low CD4+ count (<200 cells/μL) were the strongest independent factors (Table 2) in the relative survival model based on Poisson regression and independently associated with an approximately 3-fold increased risk for excess mortality (Table 2). Patients with CMV retinitis, no HAART, longer duration since AIDS diagnosis and early enrollment into LSOCA were also at statistically significantly higher risk for excess mortality. We did not find a statistically significant association between sex, age, race and HIV exposure category with excess mortality.

The number of excess deaths per 1,000 person years varied greatly depending upon the presence of the three strongest risk factors for increased excess mortality (plasma HIV RNA (viral load) >400 copies/mL, CD4+ cell count <200/μL and CMV retinitis, Table 3). For example, patients with none of these risks experienced 8 excess deaths per 1,000 person years (95% CI 5-16), versus 128 (95% CI 82-201) excess deaths per 1000 person years in patients with all three risk factors.

Discussion

Among persons who initiated HAART after having been diagnosed with AIDS, excess mortality was nearly halved between 1999 and 2007 but remained high, with 36 excess deaths per 1000 person years in 2007. Excess mortality was thus, on average, more than five times higher than rates seen among HIV-infected patients in the CASCADE study.(1) The mortality rates observed in LSOCA closely reflect those of the entire US AIDS population. The Centers for Disease Control and Prevention (CDC) reported a mortality rate of 56.3 per 1,000 person years in 1999 with a decline to 30.0 per 1,000 person years in 2007 (www.cdc.gov/hiv/topics/surveillance/resources/reports). The extent of excess mortality was linked to the presence of identifiable mortality risk factors. Calendar year, time since AIDS diagnosis, higher plasma HIV RNA (viral load) levels, lower CD4+ cell counts and diagnosis with CMV retinitis were each independent risk factors for excess mortality. Depending on the presence of the latter three risks, the extent of excess mortality seen in AIDS patients ranged from 8 extra deaths per 1,000 patient years (twice as many as observed among all HIV-infected patients) to 128 extra deaths per 1,000 patient years, a level 16 times that observed among all HIV-infected patients.(1)

Previous studies have demonstrated that HIV-related mortality rates have markedly declined as a consequence of HAART introduction and prevalent use.(6, 7, 13) Results from CASCADE further demonstrated that mortality rate declines were progressive through the first decade of the HAART era despite stability in HAART use rates.(1) Potential reasons

for continued declines in death rates include improvements in overall health care for HIV-infected persons, earlier identification of HIV infection (making earlier HAART initiation possible), trends toward earlier HAART use in general, more attention to patient adherence, as well as improvements in the efficacy and tolerability of specific antiretroviral therapies available. Our results suggest that, among patients with AIDS, the effects of improvements in HAART management might be even more pronounced. The decline in excess mortality that we observed is likely a consequence of progressive optimization of antiretroviral management (for example, timing of therapy initiation, specific drug combinations used) rather than an increased rate of HAART utilization overall; the proportion of patients receiving HAART did not change between 1999 and 2007.

The stratified analyses suggested a possible association of CD4+ count and excess mortality. Although this analysis was limited by the sample size and although the interaction between CD4+ count and year was not statistically significant in neither the main nor in two sensitivity analyses, it is remarkable that there was differential decline in excess mortality depending on CD4+ counts. A possible explanation that needs more evidence that provide by our study could be that further mortality reductions among patients with AIDS who had higher CD4+ counts becoming increasingly difficult, even with the use of more effective treatment, or is going to require substantially longer periods of follow-up.

The main limitation of our analysis was sample size. Our estimates of excess mortality suffer from a lack of precision as do the analyses stratified for CD4+ count. Another limitation of the present analyses is the focus on opportunistic infections of the eyes, which may be overrepresented among all opportunistic infections in LSOCA patients. We did not assess the (competing) risk of different opportunistic infections for excess mortality. There is, however, very limited evidence on the prevalence of opportunistic infections and their association with prognosis in AIDS patients from the USA. Furthermore, we did not explore the influence of additional factors upon mortality such as use of specific types of HAART because this was beyond the scope of this article. Finally, we focused on all-cause mortality as do most excess mortality analyses, which informs public health on changes in mortality at a population level and may serve as an index of the effectiveness of antiretroviral treatment. However, mortality among HAART treated patients clearly may not only be due to AIDS-related conditions, but also (and increasingly) is a consequence of co-morbid conditions (5, 18)

In conclusion, our study demonstrated that excess mortality among patients with AIDS was nearly halved in the HAART era and most strongly linked to stage of HIV disease. These results reflect the continuing improvements in AIDS management but also highlight that excess mortality remains about five times higher than in patients with HIV-infection but no AIDS.

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References

1. Bhaskaran K, Hamouda O, Sannes M, Boufassa F, Johnson AM, Lambert PC, et al. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. JAMA. 2008 Jul 2; 300(1):51–9. [PubMed: 18594040]
2. Ewings FM, Bhaskaran K, McLean K, Hawkins D, Fisher M, Fidler S, et al. Survival following HIV infection of a cohort followed up from seroconversion in the UK. AIDS. 2008 Jan 2; 22(1):89–95. [PubMed: 18090396]
3. Jaggy C, von Overbeck J, Ledergerber B, Schwarz C, Egger M, Rickenbach M, et al. Mortality in the Swiss HIV Cohort Study (SHCS) and the Swiss general population. Lancet. 2003 Sep 13; 362(9387):877–8. [PubMed: 13678976]
4. Lohse N, Hansen AB, Pedersen G, Kronborg G, Gerstoft J, Sorensen HT, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. Ann Intern Med. 2007 Jan 16; 146(2):87–95. [PubMed: 17227932]
5. Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr. 2006 Sep; 43(1):27–34. [PubMed: 16878047]
6. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998 Mar 26; 338(13):853–60. [PubMed: 9516219]
7. Smit C, Geskus R, Uitenbroek D, Mulder D, Van Den Hoek A, Coutinho RA, et al. Declining AIDS mortality in Amsterdam: contributions of declining HIV incidence and effective therapy. Epidemiology. 2004 Sep; 15(5):536–42. [PubMed: 15308952]
8. Jabs DA, Van Natta ML, Holbrook JT, Kempen JH, Meinert CL, Davis MD. Longitudinal study of the ocular complications of AIDS: 1. Ocular diagnoses at enrollment. Ophthalmology. 2007 Apr; 114(4):780–6. [PubMed: 17258320]
9. Jabs DA, Van Natta ML, Holbrook JT, Kempen JH, Meinert CL, Davis MD. Longitudinal study of the ocular complications of AIDS: 2. Ocular examination results at enrollment. Ophthalmology. 2007 Apr; 114(4):787–93. [PubMed: 17210182]
10. Brenner H, Hakulinen T. On crude and age-adjusted relative survival rates. J Clin Epidemiol. 2003 Dec; 56(12):1185–91. [PubMed: 14680669]
11. Dickman PC. Modeling of the cure fraction in survival studies. STATA Journal. 2007; 7(3):1–25.

12. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. Stat Med. 2004 Jan 15; 23(1):51–64. [PubMed: 14695639]
13. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet. 2002 Jul 13; 360(9327):119–29. [PubMed: 12126821]
14. Late HIV testing - 34 states, 1996-2005. MMWR Morb Mortal Wkly Rep. 2009 Jun 26; 58(24): 661–5. [PubMed: 19553901]
15. Palella FJ Jr, Deloria-Knoll M, Chmiel JS, Moorman AC, Wood KC, Greenberg AE, et al. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. Ann Intern Med. 2003 Apr 15; 138(8):620–6. [PubMed: 12693883]
16. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009 Apr 30; 360(18): 1815–26. [PubMed: 19339714]
17. HIV prevalence estimates--United States, 2006. MMWR Morb Mortal Wkly Rep. 2008 Oct 3; 57(39):1073–6. [PubMed: 18830210]
18. Friis-Moller N, Weber R, Reiss P, Thiebaut 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 May 23; 17(8):1179–93. [PubMed: 12819520]

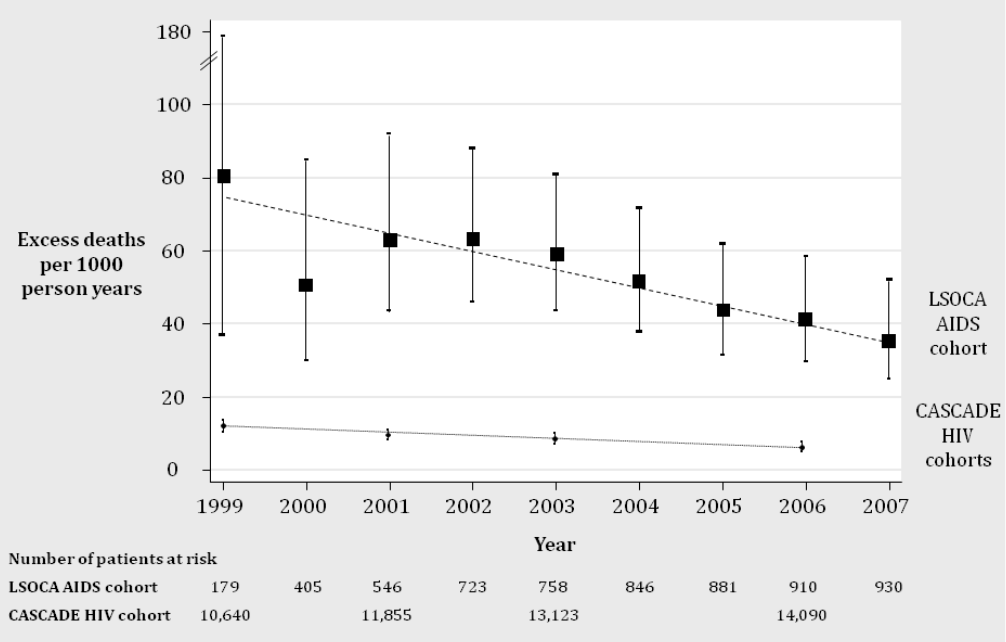

Figure 1. Decline in excess mortality between 1999 and 2007

The figure shows the decline in excess mortality in the LSOCA AIDS cohort and in the CASCADE HIV cohorts between 1999 and 2007. The upper line in the graph shows the number of excess deaths per 1,000 person years (solid rectangles) in patients with AIDS enrolled in LSOCA and 95% confidence intervals. The dashed line represents the fitted line based on a Poisson regression model. The annual decline in excess mortality averaged 8.0% per year (95% CI 3.0 to 12.7, p=0.002). The lower line in the graph shows the number of excess deaths per 1,000 person years (solid circles) in HIV patients enrolled in the CASCADE cohorts and 95% confidence intervals. The dotted line represents the fitted line based on a Poisson regression model. The annual decline in excess mortality averaged 4.8% (95% CI 3.1 to 6.5, p<0.001).

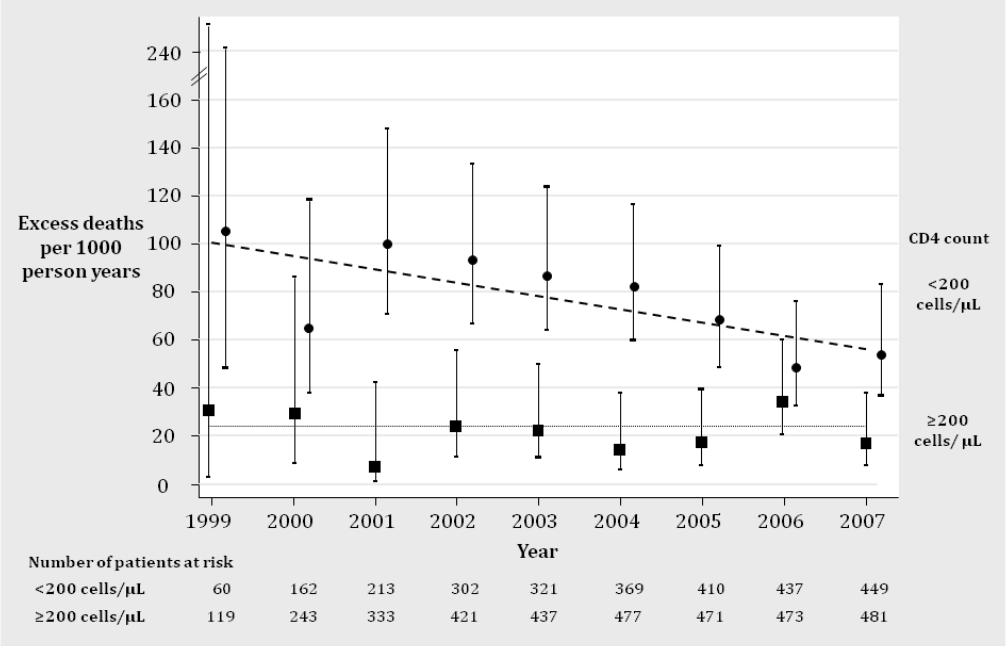

Figure 2. Decline in Excess Mortality Between 1999 and 2007, Stratified by CD4 Count at Enrollment

The figure shows the decline in excess mortality in the LSOCA AIDS cohort stratified for CD4+ count at study enrollment. The upper line in the graph shows the number of excess deaths per 1,000 person years (solid circles) in patients with low CD4+ counts and 95% confidence intervals. The dashed line represents the fitting line based on a Poisson regression model, which showed an average annual decline in excess mortality of 8.3% (95% CI 2.7 to 13.4, p=0.004). The lower line in the graph shows the number of excess deaths per 1,000 person years (solid rectangles) in patients with moderate to high CD4+ counts at study enrollment and 95% confidence intervals. The dotted line represents the fitting line based on a Poisson regression model. There was no change in excess mortality (1.4%, 95% CI -10.7 to 15.3, p=0.83). The interaction between CD4+ count status and year was not statistically significant (p=0.16).

Table 1

Patient characteristics

Patient characteristics at enrollment	Overall (n=1188)	Vital status as of end of 2007	
		Alive (n=895)	Dead (n=293)
Age groups, n (%)			
- 25-34 years	226 (19.0)	162 (18.1)	64 (21.8)
- 35-44 years	538 (45.3)	404 (45.1)	134 (45.7)
- 45-54 years	337 (28.4)	269 (30.1)	68 (23.2)
- 55-64 years	87 (7.3)	60 (6.7)	27 (9.2)
Sex, n (%)			
- male	905 (76.2)	697 (77.9)	208 (71.0)
- female	283 (23.8)	198 (22.1)	85 (29.0)
Race/Ethnicity, n (%)			
- White, non-Hispanic	462 (38.9)	357 (39.9)	105 (35.8)
- Black, non-Hispanic	492 (41.4)	352 (49.3)	140 (47.8)
- Hispanic	195 (16.4)	156 (17.4)	39 (13.3)
- Other	39 (3.3)	30 (3.4)	9 (3.0)
Time since AIDS diagnosis			
- ≤ 1 year before enrollment into LSOCA (incident AIDS)	456 (38.4)	368 (41.1)	88 (30.0)
- > 1 year before enrollment into LSOCA (prevalent AIDS)	732 (61.6)	527 (58.9)	205 (70.0)
Reason for AIDS diagnosis[#]			
- Clinical diagnosis	429 (37.7)	312 (36.6)	117 (40.9)
- CD 4 count < 200 cells/μL	710 (62.3)	541 (63.4)	169 (59.1)
HIV-exposure category, n (%)			
- Men having sex with men	495 (41.7)	390 (43.6)	105 (35.8)
- Injection drug use	86 (7.2)	60 (6.7)	26 (8.9)
- Other	607 (51.1)	445 (49.7)	162 (55.3)
CD 4 T-cell count (cells/μL)			
- < 200	687 (57.8)	455 (50.8)	232 (79.2)
- 200-499	375 (31.6)	330 (36.9)	45 (15.4)
- ≥ 500	126 (10.6)	110 (12.3)	16 (5.5)
Nadir T-cell CD 4 count (cells/μL)			
- < 100	905 (76.2)	655 (73.2)	250 (85.3)
- ≥ 100	283 (23.8)	240 (26.8)	43 (14.7)
HIV viral load at enrollment (copies/mL)			
- < 400	501 (42.2)	451 (50.4)	50 (17.1)
Cytomegalovirus retinitis, n (%)	233 (19.6)	156 (17.5)	77 (26.3)

Patient characteristics at enrollment	Overall (n=1188)	Vital status as of end of 2007	
		Alive (n=895)	Dead (n=293)
HAART treatment, n (%)	968 (81.6)	763 (85.4)	205 (70.0)

[#]Available for 1139 patients

Table 2

Independent associations of patient characteristics with excess mortality

Patient characteristic	Comparison category	Reference category	Relative risk of excess mortality (95% CI)	p-value
Sex	Female	Male	1.25 (0.92-1.71)	0.16
Age group at enrollment in years	35-44	25-34	0.89 (0.65-1.23)	0.49
	45-54		0.79 (0.54-1.15)	0.22
	55-64		1.43 (0.82-2.48)	0.20
Race	African-American	Other	1.12 (0.86-1.47)	0.41
Exposure	Injection drug use	Men having sex with men	1.35 (0.82-2.24)	0.24
	Other exposure		1.05 (0.77-1.44)	0.77
CD4+ at enrollment in cells/mL	<200	≥200	2.70 (1.87-3.89)	<0.0001
Nadir CD4+ in cells/μL *	<100	≥100	1.38 (0.92-2.07)	0.12
HIV viral load at enrollment in copies/μL	≥400	<400	3.39 (2.28-5.03)	<0.0001
CMV retinitis at enrollment	Yes	No	1.58 (1.19-2.10)	0.002
Calendar year	Per year from 1999 to 2007		0.93 (0.87-0.99)	0.025
Time since AIDS diagnosis	Per year		1.14 (1.08-1.21)	<0.0001
HAART treatment	No HAART	HAART	1.61 (1.23-2.12)	0.001

*CD4+ categories 200-499 cells/μL and ≥500 cells/μL merged into ≥200 cells/ μL because they were similarly associated with excess deaths in the multiple Poisson regression model.

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Table 3

Excess deaths per 1000 person years (95% CI) for different risk profiles at enrollment

Patients with CD4+ T-cells ≥200 (copies/μL)		
HIV viral load	CMV retinitis	No CMV retinitis
>400	44 (25-80)	26 (15-46)
≤400	14 (8-26)	8 (5-16)
Patients with CD4+ T-cells <200 (copies/μL)		
HIV viral load	CMV retinitis	No CMV retinitis
>400	128 (82-201)	98 (64-150)
≤400	32 (18-55)	23 (13-39)

Adjusted for year, sex, age, race, exposure status, time since AIDS diagnosis, nadir CD4+ T-cell count and HAART treatment