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ORIGINAL RESEARCH

Secular trends in opportunistic infections, cancers and mortality in patients with AIDS during the era of modern combination antiretroviral therapy

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Objectives

The aim of the study was to estimate the incidence of, determine risk factors for, and investigate the consequences of opportunistic infections (OIs) and malignancies among patients with the acquired immune deficiency syndrome (AIDS) in the era of modern combination antiretroviral therapy (cART).

Methods

Three enrolment periods (1998–2002, 2003–2005 and 2006–2012), corresponding to changes in predominant cART regimens, were compared among 1889 participants enrolled in a prospective cohort study, the Longitudinal Study of Ocular Complications of AIDS (LSOCA). Incidences of AIDS-related OIs and cancers were estimated. Multivariate logistic and Cox regression models were used to determine the effect of demographic and clinical characteristics on OIs and mortality.

Results

Between participants enrolled in the 1998–2002 and 2006–2012 enrolment periods, the incidence of OIs decreased from 27 per 1000 person-years (PY) to 11 per 1000 PY ($P < 0.001$), and mortality decreased from 41 per 1000 PY to 18 per 1000 PY ($P < 0.0001$), corresponding to improvements in cART regimens.

Conclusions

Improvements in cART regimens led to a progressive decline in the incidence of OIs and mortality between 1999 and 2013 among patients with AIDS in the era of modern cART.

Keywords: AIDS, AIDS-related cancer, HIV, mortality, opportunistic infection

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Introduction

With the advent of modern combination antiretroviral therapy (cART) in the mid-1990s, the incidences of HIV-associated opportunistic infections (OIs), cancers, and mortality have decreased substantially [1–15]. Despite the decline in HIV-associated OIs and cancers over the last two decades, their incidences never reached those of people without HIV infection, and they remain a leading cause of mortality and morbidity [9,16–25].

Because recommendations for cART are to start it at CD4 T-cell levels well above those at which the acquired immunodeficiency syndrome (AIDS) would be diagnosed and prior those increasing the risk for OIs, most studies demonstrating the benefits of cART on OIs involve cohorts of patients including patients with earlier stages of HIV infection. Among those at risk for OIs,

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prophylactic antimicrobial therapy [such as against *Pneumocystis jirovicii* pneumonia (PJP) and *Mycobacterium avium* complex (MAC)] also have been effective in decreasing the incidence of OIs [5,7,8]. In the modern cART era, OIs still occur, albeit at a substantially reduced rate, and are associated with lower CD4 T-cell counts and higher amounts of circulating HIV RNA in the blood (HIV load) [20,26,27]. Because most of the studies demonstrating the beneficial effect of cART on the incidence of OIs come from cohorts with earlier stages of HIV infection, there are few data on secular trends in the incidence of OIs among patients with the late stage of HIV infection, namely AIDS [28–31]. However, AIDS continues to occur, largely because of late diagnosis of HIV infection, but also because of failure in some patients to suppress HIV replication with cART [15,32–34].

The Longitudinal Study of the Ocular Complications of AIDS (LSOCA) is a 15-year prospective cohort study conducted in the era of modern cART, and is unique in that it only enrolls patients with AIDS, and with a wide range of immune function, from diverse HIV risk groups. As such, it provides a unique opportunity to evaluate the effect of cART and changes in cART regimens on the incidence of AIDS-related OIs, cancers and mortality among patients with late-stage HIV infection, namely AIDS.

Patients and methods

LSOCA is a prospective observational study of patients with AIDS conducted in the era of modern cART [35,36]. Patients aged ≥ 13 years with a diagnosis of AIDS according to the 1993 definition of the Centers for Disease Control and Prevention (CDC) case surveillance were enrolled between 1 September 1998 and 31 December 2011 at 19 centres across the USA. Only patients without an ocular OI (namely cytomegalovirus (CMV) retinitis) are included in this analysis to avoid enrolment bias. After the initial recruitment period, rolling recruitment was used to provide ongoing information on changes in the AIDS epidemic. Demographic information and a detailed medical history, including all OIs and current and previous ART, were obtained at enrolment and confirmed by record review as appropriate. A limited medical and a complete ophthalmic examination were performed [35,37]. Enrolment laboratory testing included a complete blood count, serum chemistries, and measurements of CD4 T-cell counts and HIV loads. The diagnosis of OIs was made according to the AIDS Clinical Trials Group guidelines [31], and information was collected on OIs and AIDS-related cancers; and for the purposes of this analysis, OIs and cancers were those considered AIDS-defining based on the CDC revised 1993 AIDS case surveillance definition and the 5 December 2008 CDC OI reporting guidelines (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2.htm) [38,39]. Participants were seen every 6 months in follow-up. The study and the protocol were approved by institutional review boards at all participating centres; enrolled participants provided written informed consent; and the study and procedures adhered to the Declarations of Helsinki.

Combination ART was defined as any of the following: treatment with any three antiretrovirals, one of which was either a protease inhibitor, a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a fusion, integrase or entry inhibitor; any three nucleoside reverse transcriptase inhibitors, one of which was abacavir or tenofovir (except for the regimens abacavir/tenofovir/lamivudine and didanosine/tenofovir /lamivudine); two full-dose protease inhibitors; a boosted protease inhibitor with either an NNRTI or a fusion inhibitor; or an integrase inhibitor combined with either a protease inhibitor, NNRTI, entry inhibitor or fusion inhibitor. If zidovudine and stavudine were present in the same regimen, they were removed from that regimen's total antiretroviral count because of their known antagonism [28].

In order to assess secular changes in the incidence of OIs and malignancies, participants were grouped into three recruitment periods: 1998–2002; 2003–2005 and 2006–2012. These enrolment periods were selected to coincide with changes in the predominant cART regimen being used (Table S1). Because of the initial bolus of recruitment, the initial recruitment period contained slightly over 60% of the participants.

Patient data collected and reported to the Coordinating Center as of 31 December 2012 were included in the analyses. Mortality analysed throughout the study represents all-cause mortality. Follow-up time was calculated as the time from study entry to first incidence, to death, or to 31 December 2012 for patients under active follow-up, or to the date of the last study contact for patients who were lost to follow-up. Mortality and incidence rates were calculated as the number of deaths and number of AIDS-defining conditions divided by the number of person-years at risk. Relative risks were estimated with Cox proportional hazards. Survival analyses were performed with staggered entries based on time since diagnosis of AIDS. Analyses were performed with the SAS/STAT® version 9.3 (SAS Institute, Inc., Cary, NC, USA) and STATA version 12.0 (StataCorp LP, College Station, TX, USA) software packages.

Results

Characteristics of the study population

Enrolment characteristics of the three enrolment cohorts of LSOCA are shown in Table 1. Of the 1889 participants,

1180 were enrolled in the first cohort, 329 in the second, and 380 in the third. Consistent with changes in the AIDS epidemic, there was a decrease in the proportion of participants who were white and whose HIV transmission category was male-to-male sexual contact after the first enrolment period. There was also an increase in the proportion of participants whose AIDS-defining condition was CD4 T-cell lymphopaenia, as opposed to an OI, in the third recruitment period *vs*. the first and second recruitment periods (74% *vs*. 64% and 62%, respectively; $P < 0.001$). Participants in the third recruitment period had higher enrolment CD4 T-cell counts than those in the first two recruit periods (median 282 *vs*. 174 and 197 cells/μL, respectively; $P < 0.0001$) and lower HIV loads (median 2.0 *vs*. 3.3 and 2.6 $\log_{10}$ HIV RNA copies/mL, respectively; $P < 0.0001$). Although there was an apparent increase in cART use prior to enrolment with each successive recruitment period (76% *vs*. 83% *vs*. 94%, respectively; $P < 0.0001$), there was no significant difference in the use of cART during follow-up among the three groups, and overall 97% of participants received cART during follow-up.

Incidence of opportunistic infections and AIDS-associated malignancies

There were 135 incident OI events during 13 689 person-years (PY) of observation (20 per 1000 PY). The incidence

Table 1 Patient characteristics at enrolment in the Longitudinal Study of the Ocular Complications of AIDS cohort

	Enrolment cohort				
Characteristic	**1998–2002 (*n* = 1180)**	**2003–2005 (*n* = 329)**	**2006–2012 (*n* = 380)**	**Total (*n* = 1889)**	***P*-value***
Age (years) [median (25th, 75th percentile)]	42 (37,47)	44 (40,51)	46 (40, 52)	43 (38, 49)	< 0.0001
Male (%)	81	77	80	80	0.36
Race (%)					
White	50	34	39	45	< 0.0001
African American	33	45	48	38	
Other	17	20	13	17	
HIV transmission category (%)					
Male-to-male sexual contact	57	48	51	54	0.02
Injecting drug use†	12	18	16	14	
Other	31	34	33	32	
Any insurance (%)	82	89	84	83	0.08
Time since AIDS diagnosis (years) [median (25th, 75th percentile)]	4.0 (1.6, 6.4)	5.5 (1.7, 8.7)	4.7 (1.1, 8.2)	4.3 (1.6, 7.2)	< 0.0001
AIDS diagnosis category (%)					
CD4 T-cell lymphopaenia	64	62	74	65	< 0.001
Opportunistic infection or malignancy	32	34	23	31	
Enrolment CD4 T-cell count (cells/μL)					
Median (25th, 75th percentile)	174 (66,325)	197 (104,380)	282 (124,427)	197 (80,358)	< 0.0001
Per cent of participants < 200	55	50	37	51	< 0.0001
Per cent of participants 200–500	34	35	44	36	
Per cent of participants > 500	11	14	19	13	
Nadir CD4 T-cell count (cells/μL)					
Median (25th, 75th percentile)	43 (13,112)	44 (14,101)	50 (16,133)	44 (14,115)	0.29
Per cent of participants < 50	53	53	50	53	0.24
Per cent of participants ≥ 50	47	47	40	47	
Enrolment HIV load ($\log_{10}$ copies/mL)					
Median (25th, 75th percentile)	3.3 (2.4, 4.8)	2.6 (1.9, 4.4)	2.0 (1.7, 2.7)	2.7 (1.9, 4.6)	< 0.0001
Per cent of participants < 2.6	27	42	63	37	< 0.0001
Per cent of participants 2.6–5	32	29	20	29	
Per cent of participants ≥ 5	40	29	17	33	
Maximum prior HIV load ($\log_{10}$ copies/mL)					
Median (25th, 75th percentile)	5.3 (4.7, 5.7)	5.3 (4.7, 5.8)	5.3 (4.8, 5.7)	5.3 (4.7, 5.7)	0.63
Per of cent participants < 5	11	11	10	11	0.38
Per cent of participants ≥ 5	89	89	90	90	
ART (%)					
Any ART prior to enrolment	76	83	94	81	< 0.0001
Receiving cART at enrolment	82	88	92	85	< 0.0001
Any cART during follow-up	96	96	97	97	0.14

ART, antiretroviral therapy; cART, combination antiretroviral therapy (see Methods).
**P*-values comparing three cohorts.
†The injecting drug use category includes persons with any injecting drug use.

of specific OIs by enrolment cohort is shown in Table S2 and was lower for participants enrolled in the third enrolment period than for those in the first two (11 per 1000 PY *vs.* 27 and 23 per 1000 PY, respectively; $P < 0.001$). When analysed by calendar year, the incidence of total OIs decreased from 1999 to 2013 ($P < 0.0001$) but never

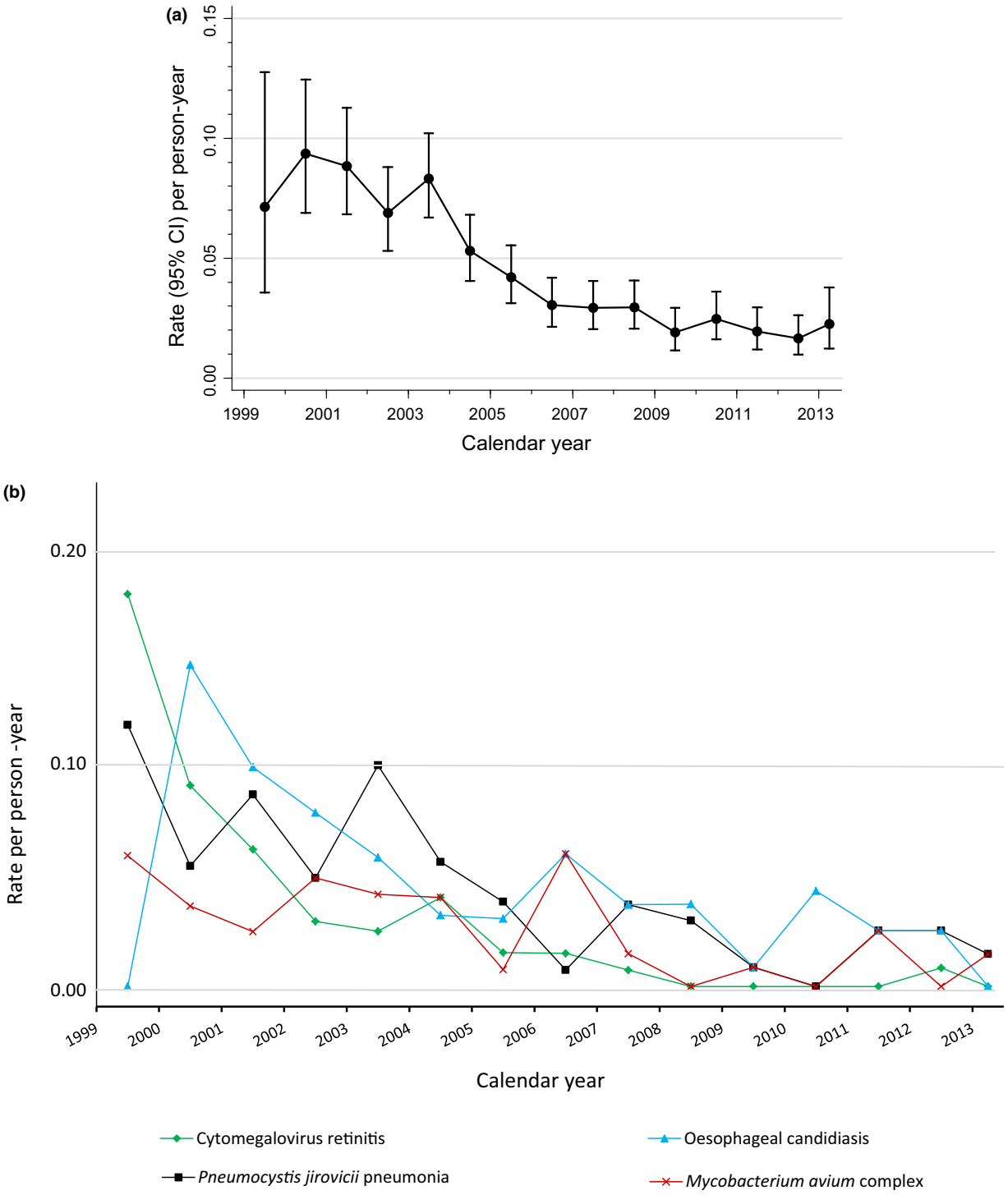

Fig. 1 Incidence of (a) total and (b) selected most common AIDS-defining opportunistic infections by calendar year. CI, confidence interval.

reached zero (Fig. 1a). The incidences of the four most common OIs (Fig. 1b) decreased from 1999 to 2007 ($P < 0.001$) and then remained constant until 2013 without reaching zero.

There were 45 incident AIDS-associated malignancies during 13 689 PY of follow-up (incidence 3.7 per 1000 PY). The cancer incidence rate decreased by successive enrolment cohort (Table 2 and Table S2). Kaposi sarcoma and lymphomas rates were similar, with a slight decline in the last cohort, and both had similarly low rates throughout.

Risk factors for incident OIs and AIDS-related malignancies are shown in Table 2. Being in the first enrolment cohort, black race, enrolment CD4 T cell count < 200 cells/μL, lower nadir CD4 T-cell count prior to enrolment, higher HIV load at enrolment, higher maximum HIV load prior to enrolment, and not being on cART were associated with increased risk for OIs (Table 2). Risk factors associated with an increased incidence of AIDS-related cancers included enrolment CD4 T-cell count < 200 cells/μL, higher HIV load at enrolment, and not being on any ART (Table 2).

The median (25%, 75%) CD4 T-cell count was 100 (23, 232) cells/μL at the first follow-up visit at which an AIDS-defining illness (any OI or cancer) was reported and 29% of the OI incidences were observed among patients with a CD4 T-cell count > 200 cells/μL. The median HIV load was 4.0 (2.3, 5.1) $\log_{10}$ copies/mL at the first follow-up visit at which an AIDS-defining illness was reported and 14% of the OI incidences were observed among patients with HIV loads < 400 copies/mL.

Mortality

The overall mortality during follow-up was 37 per 1000 PY. The mortality rate decreased from 2002 to 2013 (Fig. 2a; regression $P < 0.0001$). There was a significant decrease in mortality in the third enrolment cohort *vs.* the first two (18 per 1000 PY *vs.* 34 and 41 per 1000 PY, respectively; Fig. 2b). The relative risk (RR) for mortality comparing the first enrolment cohorts *vs.* the third was 0.46 ($P < 0.0001$). Enrolment risk factors for mortality are shown in Table 3. In addition to enrolment cohort, the presence of any AIDS-related malignancy at enrolment (RR = 1.62; $P = 0.007$) was associated with and increased mortality.

Discussion

The LSOCA cohort is unique in that it enrolled only patients with AIDS, with a wide range of immune function, and was not HIV transmission category restricted [35]. As such it is uniquely positioned to evaluate the impact of cART on AIDS-related OIs, cancers and mortality among patients with late-stage HIV infection, whereas most other cohorts evaluate these outcomes among patients including earlier stages of HIV infection. Our

Table 2 Association of clinical characteristics at enrolment with the incidence of AIDS-defining opportunistic infections (OIs) and cancers

	Any OI incidence (n = 135)		Any cancer incidence (n = 45)	
	RR*	$P^{\dagger}$	RR*	$P^{\dagger}$
Enrolment cohort				
1998–2002	Ref		Ref	
2003–2005	0.83	0.48	0.84	0.69
2006–2012	0.37	0.01	0.58	0.31
AIDS diagnosis category				
CD4 T-cell lymphopaenia	Ref		Ref	
Opportunistic infection or malignancy	0.85	0.48	1.36	0.37
Race				
White	Ref		Ref	
Black	1.65	0.008	0.66	0.22
Other	0.68	0.22	0.84	0.69
Sex				
Male	Ref		Ref	
Female	1.22	0.37	0.99	0.97
Enrolment median age				
≥ 43 years	Ref		Ref	
< 43 years	1.35	0.09	0.98	0.94
HIV transmission category				
Male-to-male sexual contact	Ref		Ref	
Injecting drug use[‡]	0.86	0.62	0.57	0.29
Other	1.06	0.79	0.58	0.13
Enrolment CD4 count				
≥ 500 cells/μL	Ref		Ref	
200–500 cells/μL	1.12	0.78	1.56	0.56
< 200 cells/μL	3.31	0.001	3.59	0.08
Nadir CD4 count				
≥ 50 cells/μL	Ref		Ref	
< 50 cells/μL	1.71	0.003	0.89	0.72
Enrolment HIV load				
< 2.6 $\log_{10}$ copies/mL	Ref		Ref	
2.6–5 $\log_{10}$ copies/mL	1.78	0.04	3.06	0.02
≥ 5 $\log_{10}$ copies/mL	4.74	< 0.0001	4.15	0.002
Maximum prior HIV load				
< 5 $\log_{10}$ copies/mL	Ref		Ref	
≥ 5 $\log_{10}$ copies/mL	2.27	0.01	2.04	0.24
Enrolment ART[§]				
No ART	Ref		Ref	
ART (no cART)	0.70	0.32	0.57	0.34
cART	0.37	< 0.0001	0.31	0.002

*Relative risk; Cox models with staggered entries based on time since diagnosis of AIDS.
[†]Likelihood ratio χ^2 P-values.
[‡]Injecting drug use category includes persons with any injecting drug use.
[§]No ART is no antiretroviral usage reported at study entry; ART (no cART) is any antiretroviral treatment that is not considered cART; cART is at least two different antiretrovirals in combination that qualify as cART according to the modern classifications (see Methods for details).

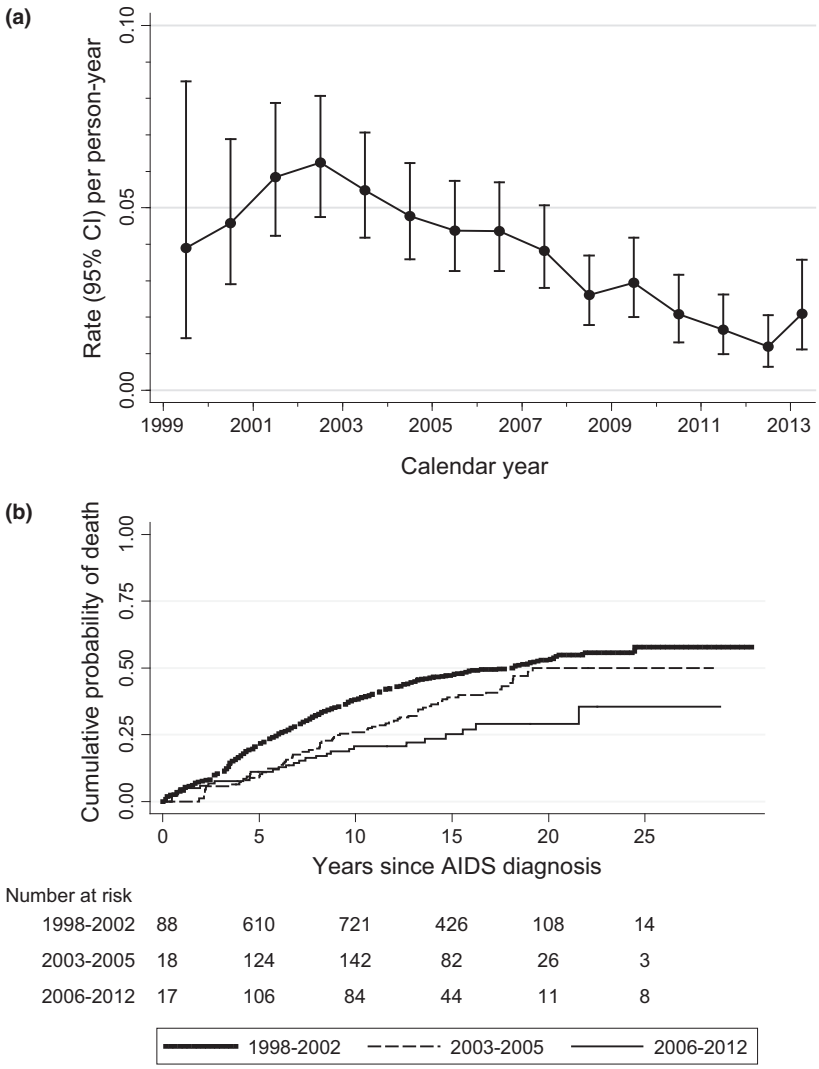

Fig. 2 Incidence of any mortality by calendar year (a) and mortality comparison among enrolment cohorts (b). CI, confidence interval.

data demonstrate a secular decline in the incidence of OIs and mortality in a cohort of patients with AIDS over the time period 1998–2013, with the largest declines in OIs occurring before 2007. Previous incidence studies of OIs in HIV-infected cohorts (i.e. not restricted to AIDS at enrolment) reported a sharp decline in the 1992–1997 period followed by a more gradual decline in 1998–2002 and low, stabilized incidences in the 2003–2007 period [7,18,20]. Despite the improvements in OI incidence and immune recovery, low, stabilized incidences of opportunistic illnesses are still evident in this cohort of patients with AIDS in the 2007–2013 calendar period. The most prevalent OIs in LSOCA were the most common OIs seen in the pre-cART era, and they continue to be the most frequently diagnosed in the modern cART era [5,6,15,40,41]. Because LSOCA enrolled only patients with AIDS, these data uniquely address the effect of cART on late-stage HIV infection. Indeed, the median nadir CD4 T-cell count prior to enrolment of 44 cells/μL indicates that the LSOCA cohort experienced profound levels of immune compromise, and that the benefits of modern cART and the secular trends in the modern cART era are present even among patients with a history of severe immune compromise. Risk factors for OIs and mortality were those expected: lower CD4 T-cell count and higher HIV load.

Patients in the third cohort were more likely to be diagnosed with AIDS based on CD4 T-cell lymphopaenia rather than based on an OI or cancer, which might in part explain the lower mortality incidence in the third cohort. However, AIDS diagnosis category did not have a significant effect

Table 3 Association of cohort, AIDS diagnosis category and AIDS-defining illnesses at enrolment with mortality

	Rate*	No. deaths/ no. at risk	RR†	*P*
Overall	37	508/1889	—	—
Enrolment cohort				
1998–2002	41	409/1180	1.00	—
2003–2005	34	72/329	0.84	0.18
2006–2012	18	27/380	0.46	0.0001
AIDS diagnosis category				
Opportunistic infection or malignancy	40	188/654	1.06	0.60
CD4 T-cell lymphopaenia	36	320/1235	1.00	—
Opportunistic infections‡				
Any opportunistic infection	39	244/862	0.99	0.98
No opportunistic infection	36	264/1027	1.00	—
Any viral infection	49	2/7	2.98	0.13
No viral infection	37	506/1882	1.00	—
Any parasitic infection	32	19/78	1.06	0.80
No parasitic infection	37	489/1811	1.00	—
Any fungal infection	39	213/746	0.99	0.96
No fungal infection	36	295/1143	1.00	—
Any mycobacterial infection	44	50/158	1.02	0.92
No mycobacterial infection	37	458/1731	1.00	—
Any cancer‡	44	43/133	1.62	0.007
No cancer	36	465/1756	1.00	—

RR, relative risk.
*Incidence per 1000 person-years.
†Cox models with staggered entries based on time since diagnosis of AIDS. Models were adjusted for age, sex, race, HIV transmissin category, nadir CD4 T-cell count, baseline CD4 T-cell count, baseline and highest recorded HIV loads, and combination antiretroviral therapy.
‡AIDS-defining opportunistic infections and cancers.

on mortality, and therefore it is unlikely to have led to a survivor bias in the last cohort. Time since AIDS diagnosis to study enrolment was significantly different among the cohorts. To avoid potential survival bias, we used a staggered entry approach anchoring survival analysis to the AIDS diagnosis date for each patient.

Although the LSOCA cohort enrolled only patients with AIDS, it was not HIV transmission category restricted [35]. Previous analyses suggested that the LSOCA cohort is relatively representative of the AIDS epidemic, with the exception of a slight under-representation of persons whose HIV transmission category is injecting drug use [35]. Therefore, LSOCA is reasonably generalizable to patients with AIDS but not to earlier stages of HIV infection. However, because of late diagnosis of HIV infection and difficulties controlling HIV replication in some patients despite good follow-up, progression to AIDS does occur [24,32,33], so information on late-stage HIV disease is important, and the LSOCA results uniquely address these patients.

There are limitations to the study. As the outcome of ocular infections (primarily CMV retinitis) was a primary aim of LSOCA, the original cohort oversampled patients with CMV retinitis. However, this analysis focused only on participants without CMV retinitis, minimizing the recruitment bias. As such, the findings should be generalizable to the AIDS epidemic in industrialized countries. The slight under-sampling of injecting drug users does not appear to limit the generalizability of the study, as injecting drug use was not a major risk factor for the outcomes of interest, and there were sufficient numbers of injecting drug users for subgroup analyses. Nevertheless, caution should be exercised in generalizing LSOCA results.

Studies have reported improvements in HIV treatment between 1996 and 2010, during which cART became less toxic, with increased efficacy and higher adherence rates leading to significant decreases in HIV RNA levels [42,43]. Our results agree with these reports which focused on the earlier stages of HIV infection and, moreover, show that the efficacy of cART regimens is getting better with time, leading to significant improvements in patient immune health and mortality even among patients with AIDS and a history of severe immune compromise.

In conclusion, this analysis of LSOCA data demonstrates a substantial decline in per-calendar-year rates of OIs among patients with AIDS, with the majority of the decline occurring between 2000 and 2009. All-cause mortality per calendar year showed a steady decline between 2002 and 2013, corresponding to a 44% overall reduction in mortality rate and a 64% reduction in mortality RR by the 2006–2012 enrolment cohort. These results demonstrate ongoing improvements in outcomes among patients with late-stage HIV disease.

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Conflicts of interest: The authors have no conflict of interest to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Three most frequent cART regimens (3+ ARVs) by year of visit (as of 31Dec 2013) in the LSOCA cohort.
Table S2. Incidence of AIDS defining illnesses by enrollment cohort.
Notes S1. LSOCA Clinical Centers - Credit Roster Key Personnel (LSOCA certified) 1997 - 2009