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Secular Trends in Opportunistic Infections, Cancers, and Mortality in Patients with AIDS during the Era of Modern Combination Antiretroviral Therapy

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Abstract

Objective: To estimate the incidence of, determine risk factors for, and 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).

Design&Methods: Comparison of three enrollment periods (1998–2002, 2003–2005, and 2006–2012), corresponding to changes in predominant cART regimens, among 1889 participants enrolled in a prospective cohort study, the Longitudinal Study of Ocular Complications of AIDS (LSOCA). Incidence of AIDS-related opportunistic infections (OIs) and cancers were estimated. Multivariate logistic and Cox regression models determined the effect of demographic and clinical characteristics on OIs and mortality.

Results: Between participants enrolled in the 1998–2002 and 2006–2012 enrollment periods, the incidence of OIs decreased from 27/1000 person-years (PY) to 11/1000 PY (P=0.001), and mortality decreased from 41/1000 PY to 18/1000 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.

Summary:

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The incidence of AIDS-defining opportunistic infections (OIs) and cancers declined between 1999 and 2013 among patients with AIDS. Low CD4+ T-cell count and high HIV load remain risk factors for OIs and mortality in modern cART era.

Keywords

HIV; AIDS; opportunistic infection; AIDS-related cancer; mortality

INTRODUCTION

With the advent of modern combination antiretroviral therapy (cART) in the mid-1990s, the incidences of human immunodeficiency virus (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 that of people without HIV, 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 which would diagnose the acquired immunodeficiency syndrome (AIDS) 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, 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 benefit of cART on the incidence of OIs come from cohorts with earlier stages of HIV, there is 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 due to late diagnosis of HIV infection, but also due to 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, 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 the late-stage HIV infection, namely AIDS.

PATIENTS and METHODS

The Longitudinal Study of the Ocular Complications of AIDS is a prospective observational study of patients with AIDS conducted in the era of modern cART [35, 36]. Patients age ≥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 dates September 1, 1998 and December 31, 2011 at 19 centers across the United States. Only patients without

an ocular OI (namely CMV-Retinitis) are included in this analysis to avoid enrollment 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 enrollment and confirmed by record review as appropriate. A limited medical and a complete ophthalmic examination were performed [35, 37]. Enrollment laboratory testing included a complete blood count, serum chemistries, CD4+ T-cell counts and HIV loads. The diagnosis of opportunistic infections was made according to the AIDS Clinical Trials Group guidelines [31], 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 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 six months in follow-up. The study and the protocol were approved by institutional review boards at all participating centers; 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: any three antiretrovirals, one of which was either a protease inhibitor, a non-nucleoside 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 due to 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 enrollment periods were selected to coincide with changes in the predominant cART regimen being used (Supplemental Table 1). 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 analyzed 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 SAS/STAT® version 9.3 (Copyright© 2002–2010. SAS Institute, Inc., Cary, NC) and Stata version 12.0 (StataCorp 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) software packages.

RESULTS

Characteristics of the Study Population

Enrollment characteristics of the three enrollment cohorts of LSOCA are shown as 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 enrollment period. There also was an increase in the proportion of participants whose AIDS-defining condition was CD4+ T cell lymphopenia, as opposed to an OI, in the third recruitment period vs. the first and second recruitment periods (74% vs. 64 and 62%, P=0.001). Participants in the third recruitment period had higher enrollment CD4+ T cells vs. the first two recruit periods (median 282 vs. 174 and 197 cells/μL, P<0.0001) and lower HIV loads (median $\log_{10}$(copies/mL) 2.0 vs. 3.3 and 2.6, P<0.0001). Although there was an apparent increase in cART use prior to enrollment with each successive recruitment period (76% vs. 83% vs. 94%, 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 of observation (20/1000 PY). The incidence of specific OIs by enrollment cohort is shown as Supplemental Table 2 and was lower for participants enrolled in the third enrollment period than in the first two (11/1000 PY vs. 27 and 23/1000 PY, P=0.001). When analyzed by calendar year, the incidence of total OIs decreased from 1999 to 2013 (P < 0.0001) but never reached zero (Figure 1A). The incidences of the four most common OIs (Figure 1B) decreased from 1999 to 2007 (P = 0.001) and then remained constant till 2013 without reaching zero.

There were 45 incident AIDS-associated malignancies during 13,689 person-years of follow-up (incidence 3.7/1000 PY). The cancer incidence rate decreased by successive enrollment cohorts (Table 2 and Supplemental Table 2). 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 enrollment cohort, black race, enrollment CD4+ T cells <200 cells/μL, lower nadir CD4+ T cells prior to enrollment, higher HIV load at enrollment, higher maximum HIV load prior to enrollment, and not being on cART therapy were associated with increased risk for OIs (Table 2). Risk factors associated with an increased incidence of AIDS related cancers included enrollment CD4+ T cells <200 cells/μL, higher HIV load at enrollment, and not being on any anti-retroviral therapy (Table 2).

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

defining illness and 14% of the OI incidences were observed among patients with HIV loads < 400 copies/mL.

Mortality

The overall mortality during follow-up was 37/1000 PY. The mortality rate decreased from 2002 to 2013 (Figure 2A; regression P<0.0001). There was a significant decrease in mortality in the third enrollment cohort vs. the first two (18/1000 PY vs. 34/1000 PY and 41/1000 PY, respectively, Figure 2B). The relative risk (RR) for mortality comparing the first enrollment cohorts vs. the third was 0.46 (P=0.0001). Enrollment risk factors for mortality are shown in Table 3. In addition to enrollment cohort, presence of any AIDS-related malignancy at enrollment (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 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 enrollment) reported a sharp decline in the 1992–1997 period followed by a more gradual decline in 1998–2002 and low-level stabilized incidences in the 2003–2007 period [7, 18, 20]. Despite the improvements in OI incidence and immune recovery, low-level 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 enrollment 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 opportunistic infections and mortality were those expected: lower CD4+ T cells and higher HIV load.

Patients in the third cohort were more likely to be diagnosed with AIDS based on CD4+T-cell lymphopenia 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 on mortality, therefore it is unlikely to lead to a survivor bias in the last cohort. Times since AIDS diagnosis to study enrollment 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 injection 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 and difficulties controlling HIV replication in some patients despite good follow-up, progression to AIDS does occur [24, 32, 33], so that 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 AIDS epidemic in the industrialized countries. The slight under-sampling of injection drug users does not appear to limit the generalizability of the study as injection drug use was not a major risk factor for the outcomes of interest, and there were sufficient numbers of injection drug users for subgroup analyses. Nevertheless, caution should be taken in generalizing LSOCA results.

Studies have reported improvements in HIV treatment between 1996–2010, 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 that focused on the earlier stages of HIV infection, and moreover, show that the efficacy of cART regimens are getting better with time leading to significant improvements in patient immune health and mortality even among patients with AIDS and history of severe immune compromise.

In conclusion, this analysis of LSOCA data demonstrates a substantial decline in per-calendar-year rates for opportunistic infections 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 relative risk by the 2006–2012 enrollment cohort. These results demonstrate ongoing improvements in the outcomes among patients with late-stage HIV disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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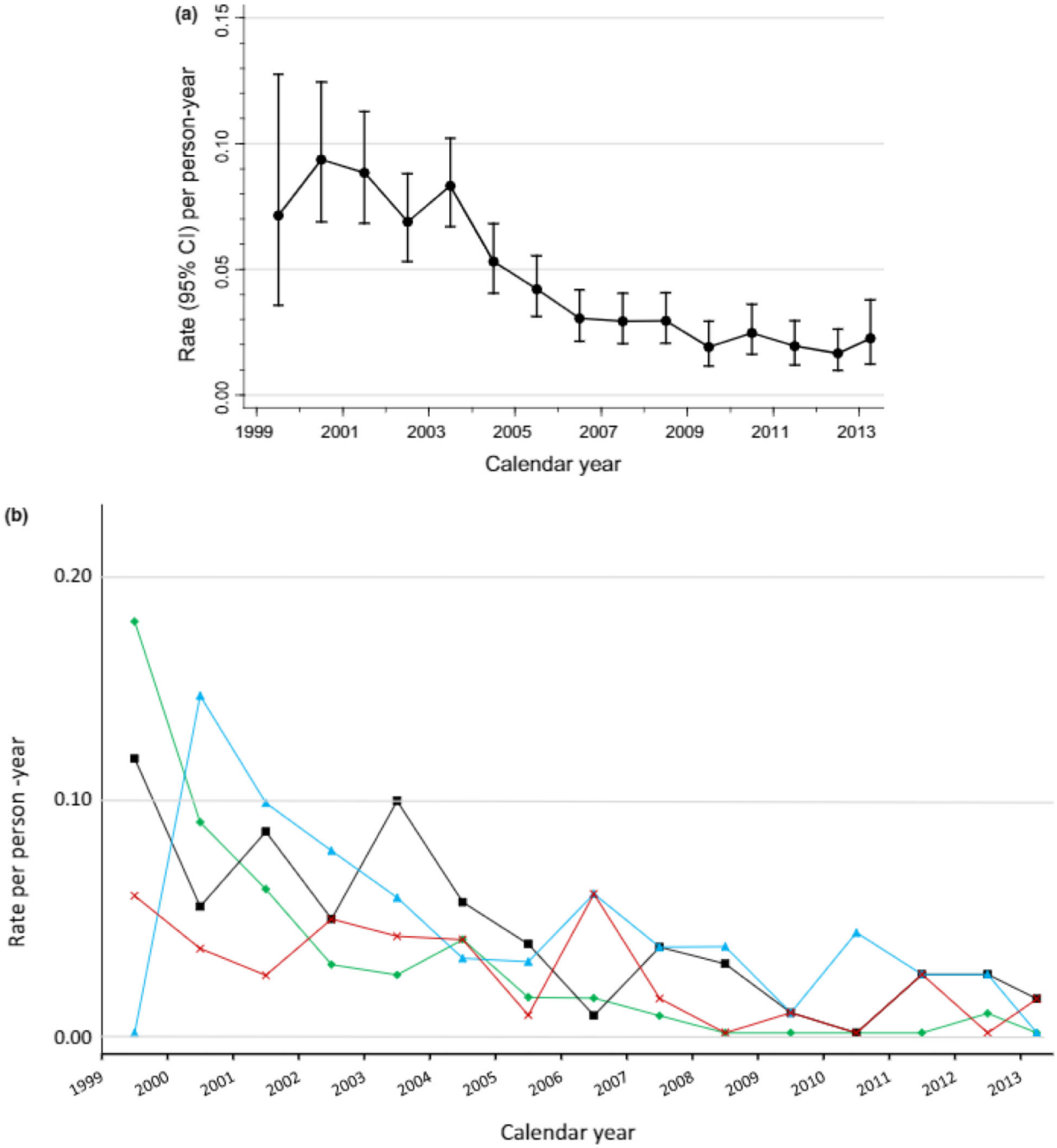

Fig. 1.

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

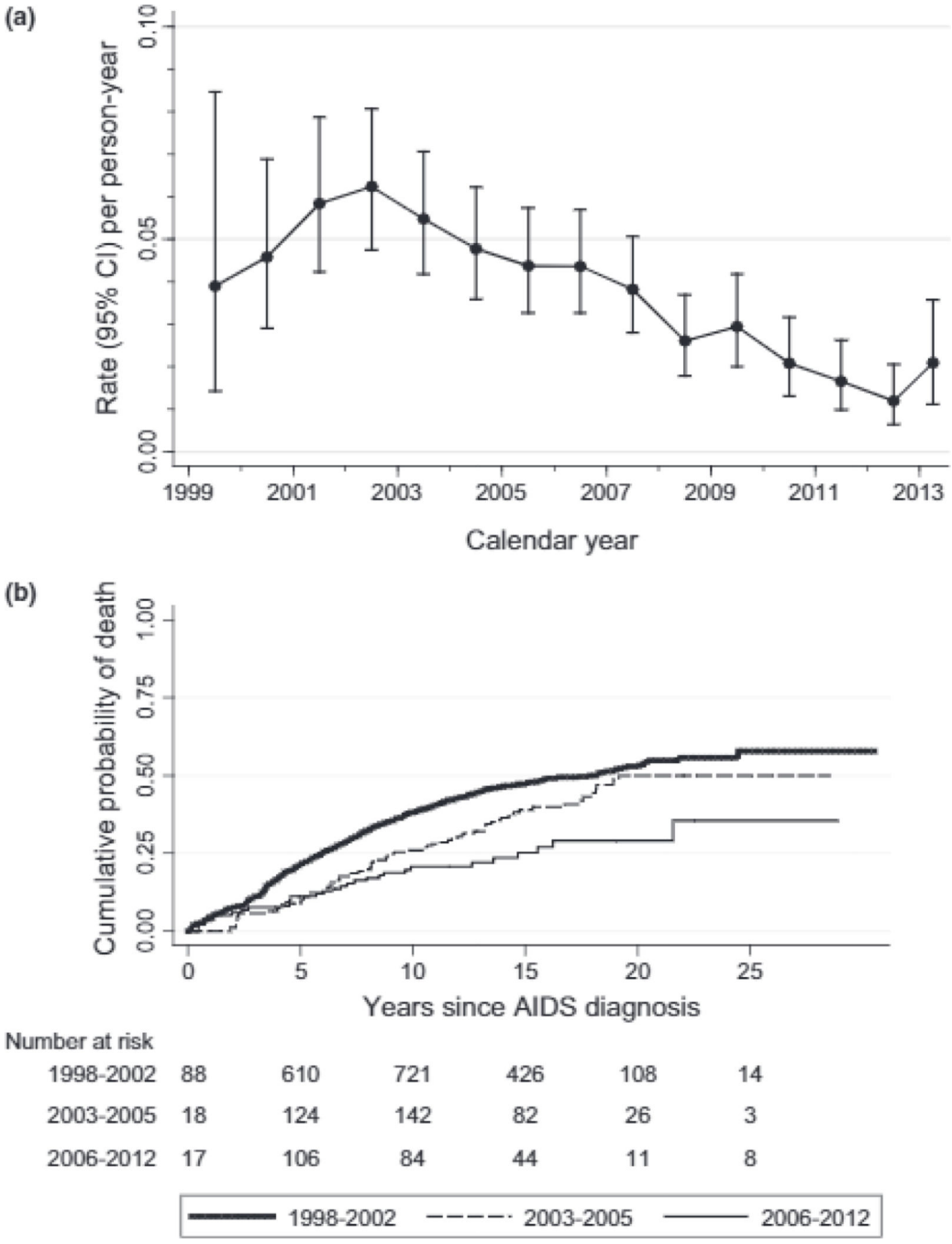

Fig. 2.

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

Table 1.

Patient characteristics at enrollment in the Longitudinal Study of the Ocular Complications of AIDS cohort

	Enrollment Cohort				
	1998–2002	2003–2005	2006–2012	Total	P-value[a]
Number patients	**1180**	**329**	**380**	**1889**	
Median age, years (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 (%)					< 0.0001
White	50	34	39	45	
African American	33	45	48	38	
Other	17	20	13	17	
HIV transmission category (%)					0.02
Male to male sexual contact	57	48	51	54	
Injection drug use[b]	12	18	16	14	
Other	31	34	33	32	
Any insurance (%)	82	89	84	83	0.08
Median time since AIDS diagnosis, years (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 (%)					0.001
CD4+ T-cell lymphopenia	64	62	74	65	
Opportunistic infection or malignancy	32	34	23	31	
Enrollment CD4+ T-cells (cells/uL)					
Median(25th, 75th percentile)	174 (66,325)	197 (104,380)	282 (124,427)	197 (80,358)	< 0.0001
Percent participants <200	55	50	37	51	<0.0001
Percent participants 200–500	34	35	44	36	
Percent participants >500	11	14	19	13	
Nadir CD4+ T-cells (cells/uL)					
Median (25th, 75th percentile)	43 (13,112)	44 (14,101)	50 (16,133)	44 (14,115)	0.29
Percent participants <50	53	53	50	53	0.24
Percent participants ≥50	47	47	40	47	
Enrollment HIV load (log10[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
Percent participants <2.6	27	42	63	37	< 0.0001
Percent participants 2.6–5	32	29	20	29	
Percent 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
Percent participants <5	11	11	10	11	0.38
Percent participants ≥5	89	89	90	90	
Antiretroviral therapy (%)					
Any ART prior to enrollment[c]	76	83	94	81	< 0.0001

	Enrollment Cohort				
	1998–2002	2003–2005	2006–2012	Total	P-value[a]
Number patients	**1180**	**329**	**380**	**1889**	
Receiving cART at enrollment[c]	82	88	92	85	< 0.0001
Any cART during follow-up[c]	96	96	97	97	0.14

[a] P-values comparing three cohorts.

[b] Injection drug use category includes persons with any injection drug use.

[c] ART = antiretroviral therapy. cART = combination antiretroviral therapy (see Methods).

Table 2.

Association of clinical characteristics at enrollment with incidence of AIDS defining opportunistic infections and cancers

	Any OI Incidence (n=135)		Any Cancer Incidence (n=45)	
	RR[b]	P[b]	RR[b]	P[b]
Enrollment 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 lymphopenia	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
Enrollment median age				
≥43	Ref		Ref	
<43	1.35	0.09	0.98	0.94
HIV transmission category Male to male sexual contact	Ref		Ref	
Injection drug use[c]	0.86	0.62	0.57	0.29
Other	1.06	0.79	0.58	0.13
Enrollment CD4+T-Cells (cells/uL)				
≥500	Ref		Ref	
200–500	1.12	0.78	1.56	0.56
<200	3.31	0.001	3.59	0.08
Nadir CD4+T-Cells (cells/uL)				
≥50	Ref		Ref	
<50	1.71	0.003	0.89	0.72
Enrollment HIV load (log10[copies/ml])				
< 2.6	Ref		Ref	
2.6–5	1.78	0.04	3.06	0.02
≥ 5	4.74	<.0001	4.15	0.002
Maximum prior HIV load (log10[copies/ml])				
<5	Ref		Ref	
≥ 5	2.27	0.01	2.04	0.24
Enrollment ART[d]				

	Any OI Incidence (n=135)		Any Cancer Incidence (n=45)	
	RR[b]	P[b]	RR[b]	P[b]
No ART	Ref		Ref	
ART (no cART)	0.70	0.32	0.57	0.34
cART	0.37	<.0001	0.31	0.002

[a] Likelihood ratio Chi square P values.

[b] Relative Risk. Cox models with staggered entries based on time since diagnosis of AIDS

[c] Injection drug use category includes persons with any injection drug use.

[d] No ART is no anti-retroviral usage reported at study entry; ART is any anti-retroviral treatment that is not considered cART; cART regimen is at least 2 different ART in combination that qualifies modern cART classifications (see Methods for details).

Table 3.

Association of cohort, AIDS diagnosis category and AIDS defining illnesses at enrollment with mortality.

	Rate[a]	No.Deaths/No. at risk	RR[b]	P
Overall	37	508/1889	—	—
Enrollment 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 lymphopenia	36	320/1235	1.00	—
Opportunistic Infections[c]				
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[c]	44	43/133	1.62	0.007
No cancer	36	465/1756	1.00	—

[a] Incidence per 1000 person years.

[b] Cox models with staggered entries based on time since diagnosis of AIDS. Models adjusted for age, sex, race, HIV transmissin category, nadir CD4+ T-cell count, baseline CD4+ T-cell count, baseline and highest recorded HIV load, and cART.

[c] AIDS defining opportunistic infectins and cancers.