

Improving survival following AIDS in Australia, 1991–1996

Yueming Li, Ann M. McDonald, Gregory J. Dore and John M. Kaldor
for the National HIV Surveillance Committee*

Objective: To describe the pattern of survival following AIDS.

Design: National surveillance for AIDS diagnoses.

Methods: AIDS cases in adults/adolescents (aged 13 years or older at AIDS diagnosis) and deaths following AIDS were notified to the national HIV surveillance centre by the diagnosing doctor through State/Territory health authorities. The date of last medical contact for each case living with AIDS was updated annually.

Results: By 30 June 1999, 4814 AIDS cases, diagnosed in Australia in 1991–1996, and 3193 deaths following AIDS had been notified to the National AIDS Registry. Median survival following AIDS was 17.7 months. Survival following AIDS increased from 16.0 months in 1991 to 27.7 months in 1996. Factors independently associated with improved survival were year of AIDS diagnosis, late HIV diagnosis, CD4+ cell count greater than 50×10^6 cells/l, age of less than 45 years and presentation with *Pneumocystis carinii* pneumonia only or Kaposi's sarcoma only. The risk of death declined over time when the initial AIDS-defining illness was *Pneumocystis carinii* pneumonia only [adjusted hazard ratio (AHR) = 0.91, $P < 0.0005$]; other opportunistic infections (AHR, 0.88; $P < 0.0005$); Kaposi's sarcoma only (AHR, 0.92; $P = 0.025$); and central nervous system conditions (HIV encephalopathy, cryptococcosis, toxoplasmosis) (AHR, 0.92; $P = 0.012$). No time trend was observed for survival following diagnoses of non-Hodgkin's lymphoma or other multiple illnesses.

Conclusions: Survival following AIDS has improved in Australia, especially among cases diagnosed in 1995 and 1996. Temporal improvements in survival following AIDS were coincident with the introduction of combination antiretroviral treatment for HIV infection and suggest that treatment is effective in limiting disease progression among people with advanced HIV infection.

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Introduction

The impact of improved antiretroviral therapy on HIV disease progression has been examined in several industrialized countries. Most commonly, reductions in AIDS incidence and mortality from 1995 have been

used to support a population level benefit of combination antiretroviral therapy. In Australia, the annual number of deaths following AIDS has declined from a peak of 735 in 1994 to an estimated 509 in 1996, and 170 in 1998, adjusted for reporting delay [1]. Similar decreases in AIDS deaths have been reported in other

From the National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Darlinghurst, New South Wales, Australia. *See Appendix.

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Correspondence to Professor J. Kaldor, National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, 376 Victoria Street, Darlinghurst, NSW 2010, Australia.

Tel: +61 2 9332 4648; fax: +61 2 9332 1837; e-mail: jkaldor@nchecr.unsw.edu.au

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countries including the United States [2] and Canada [3].

Although the relative contributions of improved anti-retroviral therapy and declining HIV incidence from the mid-1980s on declining AIDS incidence in Australia have been estimated [4], recent trends in survival among people with AIDS have not been examined. Studies that have demonstrated benefits of combination antiretroviral therapy on HIV disease progression have generally been among observational clinic-based cohorts [5–9]. Only two studies to date, from separate regions of Italy [10,11] have examined recent changes in survival among people with AIDS at a population level.

Among AIDS cases diagnosed in Australia in 1982–1991, median survival following AIDS was 14.3 months; median survival gradually increased from 6.6 months for cases diagnosed in 1982–1985 to 16.4 months for cases diagnosed in 1990 [12]. Here we report survival following AIDS for cases diagnosed in Australia in the years 1991–1996.

Methods

National surveillance procedures for AIDS have been previously described [13]. Briefly, AIDS is a notifiable condition in each State/Territory health jurisdiction in Australia; the diagnosing doctor notifies AIDS cases to the State/Territory health authority, which then forwards the notifications to the national HIV surveillance centre for entry onto the National AIDS Registry. Death following AIDS is also notified primarily by the treating doctor; in some health jurisdictions, death following AIDS is identified through linkage with the State/Territory Register of Deaths.

Prior to 1993, the US Centers for Disease Control AIDS surveillance case definition was applied in Australia [14]; the 1993 revised case definition has also been applied except for the criteria based solely on a CD4+ cell count of less than 200×10^6 cells/l [15].

Information sought on each AIDS case includes the sex and date of birth of the person, the date of first HIV and AIDS diagnosis in Australia, initial AIDS-defining illness(es), CD4+ cell count at AIDS diagnosis, date of last medical contact and date of death following AIDS. Each year, State/Territory health authorities update the date of last medical contact for people living with AIDS.

Statistical methods

Survival following AIDS was measured from the date of diagnosis of the initial AIDS-defining illness to the

date of death or date of last medical contact if death had not been reported by 30 June 1999. Cases without a date of last contact or date of death following AIDS diagnosis were excluded. Median survival times were calculated using the Kaplan–Meier method. Differences in median survival were assessed using the log-rank test. Multivariate analyses of association between covariates and survival time were assessed using Cox proportional hazards regression [16].

Time trends in survival following specific categories of initial AIDS-defining illnesses were assessed using Cox models. AIDS illnesses were grouped as *Pneumocystis carinii* pneumonia only, other opportunistic infections (OI) only, Kaposi's sarcoma (KS) only, non-Hodgkin's lymphoma only, central nervous system (CNS) conditions (HIV encephalopathy, toxoplasmosis and cryptococcosis) and cases with other single or multiple illnesses.

Results

By 30 June 1999, 4814 adults/adolescents (13 years or older at AIDS diagnosis) diagnosed with AIDS from January 1991 to December 1996 and 3193 deaths following AIDS had been reported to the National AIDS Registry in Australia. Table 1 summarizes the characteristics of the 4691 AIDS cases (97.4%) with information on vital status after AIDS diagnosis. The vast majority of AIDS cases (95.7%) was male; 73.2% were aged 26–45 years. AIDS incidence increased from 785 cases in 1991 to a peak of 912 cases in 1994 and then declined to 625 cases in 1996. Date of HIV diagnosis was reported for 4425 (94.3%) AIDS cases and of these, 802 (18.1%) were diagnosed with AIDS within 3 months of HIV diagnosis ('late' HIV diagnosis). Of the 4145 (88.4%) cases with a reported CD4+ cell count at AIDS diagnosis, about half (49.5%) had a count of 50×10^6 cells/l or less. The categories of initial AIDS-defining illness most frequently diagnosed were opportunistic illnesses other than *Pneumocystis carinii* pneumonia (40.5%), *Pneumocystis carinii* pneumonia only (24%) and Kaposi's sarcoma only (11.2%).

Among cases with information on vital status following AIDS diagnosis, 80% (2652 of 3304) of those diagnosed in 1991–1994 were reported to have died whereas less than 40% (541 of 1387) of those diagnosed in 1995–1996 had died following AIDS. Of the 123 cases without information on vital status following AIDS diagnosis, almost half were diagnosed in the last 2 years of the 6-year reporting period. Comparison of 1387 cases with information on vital status with 61 cases without information on vital status (hence excluded from the survival analysis) following AIDS diagnosis in

Table 1. Median survival (months) following AIDS diagnosis in Australia, 1991–1996, and factors associated with survival

	No. AIDS	No. death	Median survival (95% CI)	AHR (95% CI)	P
Total	4691	3193	17.7 (16.9–18.4)		
Sex					0.965
Male	4491	3051	17.7 (16.9–18.5)	1.00	
Female	200	142	16.4 (12.0–20.8)	1.00 (0.85–1.19)	
Age at AIDS (years)					
13–25	231	147	23.6 (18.2–28.9)	1.00	
26–45	3433	2284	18.6 (17.7–19.5)	1.15 (0.97–1.36)	0.108
> 45	1027	762	13.5 (12.0–14.9)	1.54 (1.29–1.85)	< 0.0005
Year of AIDS diagnosis					
1991	785	716	16.0 (14.4–17.6)	1.00	
1992	770	673	16.7 (15.3–18.0)	0.97 (0.87–1.08)	0.533
1993	837	661	16.7 (14.9–18.4)	0.87 (0.78–0.97)	0.014
1994	912	602	18.1 (16.0–20.2)	0.82 (0.74–0.92)	0.001
1995	762	360	19.7 (16.8–22.5)	0.64 (0.57–0.73)	< 0.0005
1996	625	181	27.7 (22.9–32.5)	0.60 (0.51–0.71)	< 0.0005
CD4 at AIDS					
≤ 50	2050	1565	13.6 (12.9–14.3)	1.00	
> 50	2095	1278	23.4 (22.3–24.6)	0.53 (0.49–0.58)	< 0.0005
Unknown	546	350	17.6 (15.0–20.3)	0.71 (0.62–0.81)	< 0.0005
Time from HIV diagnosis					
≤ 3 months	802	520	21.0 (19.5–22.6)	1.00	
> 3 months	3623	2519	16.8 (15.9–17.6)	1.22 (1.11–1.35)	< 0.0005
Unknown	266	154	19.1 (13.8–24.3)	0.87 (0.71–1.06)	0.159
Initial AIDS-defining illness					
PCP only	1124	755	21.8 (20.5–23.1)	1.00	
Other OI, not cancer or CNS	1900	1252	16.8 (15.6–18.0)	1.17 (1.06–1.28)	0.001
Kaposi's sarcoma only	527	332	21.3 (19.0–23.6)	1.01 (0.88–1.15)	0.934
Non-Hodgkin's lymphoma only	194	152	7.2 (5.0–9.4)	2.20 (1.84–2.63)	< 0.0005
CNS-associated illnesses	513	371	13.5 (11.6–15.5)	1.36 (1.20–1.54)	< 0.0005
Other single or multiple illnesses	433	331	12.4 (10.5–14.2)	1.44 (1.26–1.64)	< 0.0005

AHR, adjusted hazard ratio – adjusted for all the variables included in Table 1; CI, confidence interval; PCP, *Pneumocystis carinii* pneumonia; OI, opportunistic infection; CNS, central nervous system.

1995–1996 indicated that the excluded cases had a significantly higher CD4+ cell count at diagnosis (80×10^6 cells/l) than cases included in the analysis (60×10^6 cells/l) ($P = 0.04$); no difference was observed between cases included and those excluded from the survival analysis with respect to sex ($P = 0.51$), median age at AIDS diagnosis (37 years for both included and excluded cases, $P = 0.76$), time from HIV diagnosis (16.4% of included and excluded cases were newly diagnosed with HIV infection within 3 months of AIDS diagnosis), and initial AIDS-defining illness ($P = 0.90$).

Median survival following AIDS diagnosis in 1991–1996 was 17.7 months.

Cases for which HIV infection was diagnosed more than 3 months prior to AIDS diagnosis had a higher risk of death than cases with late HIV diagnosis [adjusted hazard ratio (AHR) = 1.22; $P < 0.0005$]. Age of 45 years or less ($P < 0.0005$) and a CD4+ cell count of greater than 50×10^6 cells/l at AIDS diagnosis ($P < 0.0005$) was independently associated with improved survival (Table 1). Cases with a diagnosis of *Pneumocystis carinii* pneumonia only or KS only had a lower risk of death than cases with other initial AIDS-defining illnesses. The AHR increased from 1.17 ($P = 0.001$) for cases with opportunistic infections

other than *Pneumocystis carinii* pneumonia to 2.20 ($P < 0.0005$) for cases with non-Hodgkin's lymphoma. A CD4+ cell count above 50×10^6 cells/l at AIDS diagnosis was associated with improved survival for every category of initial AIDS-defining illness.

Although survival following AIDS increased significantly from 16.0 months in 1991 to 18.1 months in 1994, the most marked annual increases in median survival of 1.6 months and 8 months occurred in 1994–1995 and in 1995–1996, respectively (Fig. 1). In multivariate analysis (Table 1), risk of death among AIDS cases diagnosed in 1995 and 1996 decreased by 36 and 40%, respectively, compared with cases diagnosed in 1991. The pattern of a gradual increase in survival for cases diagnosed prior to 1994 followed by a more rapid increase among cases diagnosed in 1995 and 1996 was observed for all categories of initial AIDS-defining illness except for those cases with non-Hodgkin's lymphoma (Table 2). The adjusted decrease in the risk of death was estimated at about 10% each year.

Discussion

Analysis of national, population-based AIDS surveillance data in Australia has demonstrated that survival

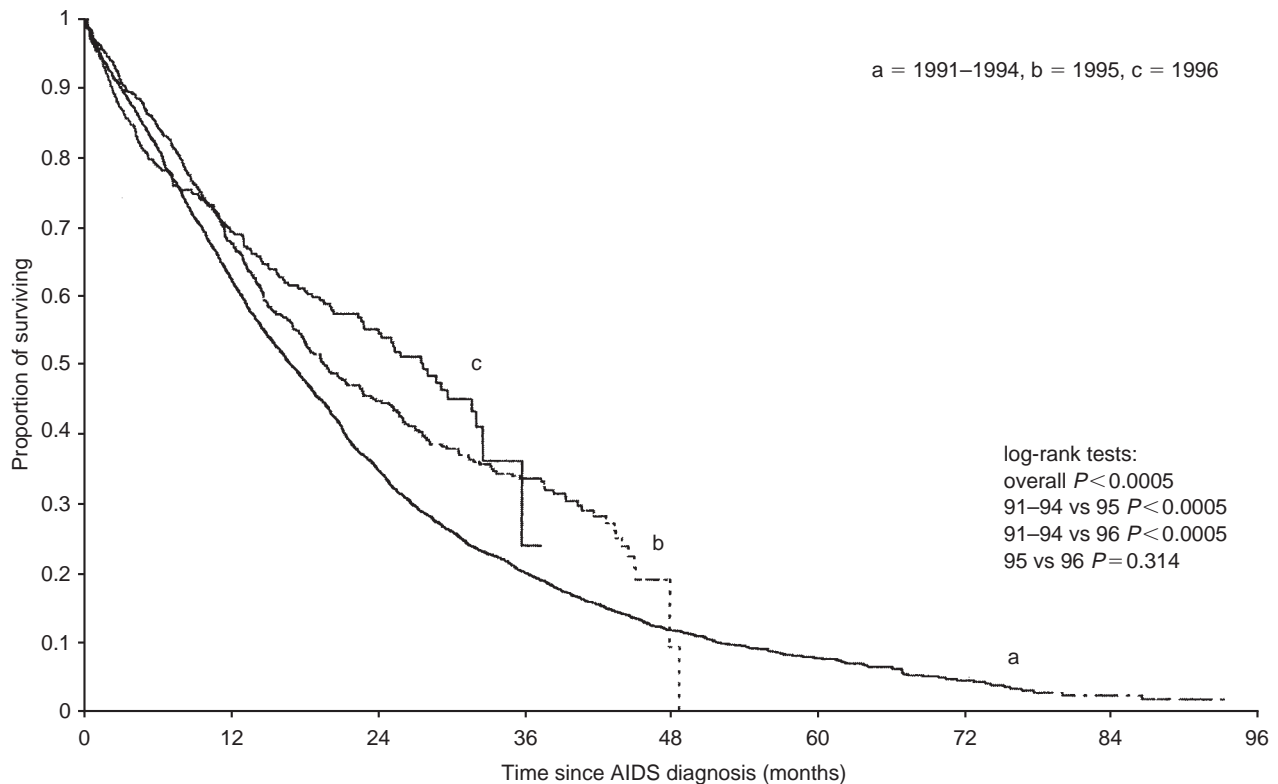


Fig. 1. Survival following AIDS by year of AIDS diagnosis, 1991-1996, Australia.

following AIDS has improved significantly, especially among AIDS cases diagnosed in 1995 and 1996. The observed improvements in survival following AIDS in Australia are consistent with recent studies from two geographic regions in Italy [10,11]. In the Tuscany region, median survival following AIDS increased from 11 to 13 months between 1987 and 1994 to almost 18 months among people diagnosed with AIDS in 1995 [10]. The study from the Lazio region demonstrated improved AIDS survival from the second half of 1995, with further improvement in 1996 [11].

Our results may have been influenced by exclusion from analysis of cases diagnosed in recent years which did not have information on vital status following AIDS diagnosis, by completeness of notification of AIDS and by reporting delay. AIDS cases diagnosed in 1995-1996 which were excluded from analysis had a significantly higher CD4+ cell count than cases included in the analysis, suggesting that survival for cases diagnosed in 1995 and 1996 may in fact be underestimated. Linkage of records of Kaposi's sarcoma reported to a cancer registry, in a State where 60% of Australian AIDS diagnoses are made, and the National AIDS Registry, indicated that 98% of cases of Kaposi's sarcoma had been notified as having AIDS [17]. Biases due to reporting delay have been minimized by allowing a follow-up period of at least 2.5 years. By 31 March 1999, less than 2% of AIDS cases diagnosed in

1996 and less than 1% of deaths following AIDS were estimated as having not yet been notified [1]. Our analysis of factors which influence survival following AIDS may also have been limited by lack of information on the occurrence of AIDS-defining illnesses subsequent to the initial illness.

The temporal improvements in survival following AIDS have occurred at a time of rapidly changing clinical practice in Australia. Until the end of 1994, antiretroviral therapy was based on the nucleoside analogues zidovudine, didanosine and zalcitabine, usually as monotherapy [1]. Lamivudine has been available since early 1995 for people with advanced HIV infection. Protease inhibitors became widely available from mid-1996. In a large cohort of gay men with HIV infection in Sydney, use of triple combination antiretroviral therapy increased steadily from 11.7% in the first half of 1996 to 72% in the second half of 1997; use of a protease inhibitor also increased from 10.6% in the first half of 1996 to 68% in the second half of 1997 [1].

The absence of information on antiretroviral therapy for individual AIDS cases in Australia precludes a direct assessment of therapeutic benefit. However, the temporal association between increased uptake of combination antiretroviral therapy including lamivudine from 1995, and the substantial improvements in survival

Table 2. Median survival following AIDS diagnosis in Australia, 1991–1996, by year and category of initial AIDS-defining illness.

Type of AIDS illness	Median survival (months) (95% CI)						1996	AHR* (95% CI)	P*
	1991	1992	1993	1994	1995	1996			
PCP only	21.6 (19.1–24.0)	20.2 (18.0–22.4)	20.2 (17.8–22.5)	22.4 (19.4–25.5)	30.7 (20.8–40.6)	ND	0.91 (0.86–0.95)	< 0.0005	
Other OI, not cancer or CNS	14.0 (11.7–16.2)	14.8 (12.5–17.2)	16.1 (13.8–18.5)	17.9 (15.4–20.4)	18.0 (13.6–22.3)	29.2 (24.4–34.0)	0.88 (0.85–0.92)	< 0.0005	
Kaposi's sarcoma only	19.1 (14.9–23.3)	20.7 (16.6–24.9)	22.2 (15.1–29.3)	21.2 (16.5–26.0)	21.5 (13.6–29.4)	32.6 (ND)	0.92 (0.85–0.99)	0.025	
Non-Hodgkin's lymphoma only	4.9 (0.0–13.2)	8.0 (0.0–21.5)	7.5 (4.1–10.9)	6.7 (1.9–11.4)	8.0 (5.9–10.1)	7.8 (1.9–13.7)	1.02 (0.93–1.13)	0.639	
CNS	12.0 (8.4–15.6)	13.3 (10.7–15.9)	13.5 (11.0–16.0)	11.6 (6.2–17.0)	19.4 (10.8–28.0)	22.4 (19.3–25.4)	0.92 (0.86–0.98)	0.012	
Other single or multiple illnesses	9.3 (6.2–12.5)	11.5 (9.4–13.6)	13.2 (11.7–14.7)	9.9 (2.8–17.0)	13.8 (9.7–18.0)	27.6 (2.8–52.3)	0.93 (0.86–1.00)	0.063	

*Adjusted hazards ratio (AHR) and *P* value for time trends. Factors adjusted for were sex, age and CD4+ cell counts at AIDS diagnosis, time from HIV diagnosis to AIDS diagnosis. ND, not determined; CI, confidence interval; PCP, *Pneumocystis carinii* pneumonia; OI, opportunistic infection; CNS, central nervous system.

following AIDS in 1995 and 1996, suggest that combination antiretroviral treatments have contributed to improved survival. Our data do not yet allow an assessment of the effect of protease inhibitors on survival following AIDS. Results available through a network of hospitals and clinics in the United States show that the risk of death following AIDS was lowest among cases prescribed triple combination therapy compared with cases prescribed dual- or monotherapy [18].

Improved survival among cases with late HIV diagnosis compared to cases for which HIV infection was diagnosed at least 3 months prior to AIDS may be partly attributable to limited use of antiretroviral therapy prior to AIDS. Cases with late HIV diagnosis had the opportunity of, at most, 3 months treatment for HIV infection prior to AIDS and potentially had a shorter period of time for development of drug-resistant viruses [19,20]. AIDS cases diagnosed late in the course of HIV infection could also benefit from advances in antiretroviral and prophylactic treatment for HIV infection without prior use of treatments which only partially suppressed viral replication. Increased survival of cases of late HIV diagnosis is consistent with the greater benefit of combination antiretroviral therapy observed among cases not previously exposed to therapy [21,22,23].

Factors other than calendar year of AIDS diagnosis and timing of HIV diagnosis relative to AIDS diagnosis which influenced survival following AIDS in Australia were age and CD4+ cell count at AIDS diagnosis, and initial AIDS-defining illness. Poorer AIDS survival for older age groups and those with more severe immunosuppression is consistent with previous studies of HIV disease progression [10–12,18,23]. AIDS survival was poorest for cases diagnosed with non-Hodgkin's lymphoma only. Furthermore, non-Hodgkin's lymphoma was the only initial AIDS-defining illness with no observed improvement in survival over time, suggesting that antiretroviral therapy had limited effectiveness in improving survival in these cases.

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Appendix

The National HIV Surveillance Committee comprises: Ms Irene Passaris (Australian Capital Territory); Mr Robert Menzies (New South Wales); Dr Jan Savage (Northern Territory); Dr Hugo Ree (Queensland); Ms Therese Davey (South Australia); Mr Neil Cremasco (Tasmania); Ms Cathy Keenan (Victoria); Dr Gary Dowse (Western Australia); Professor John Kaldor and Ann McDonald (National Centre in HIV Epidemiology and Clinical Research).