Natural history and mortality in HIV-positive individuals living in resource-poor settings:

A literature review

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Introduction

The increasingly widespread use since 1996 of highly active antiretroviral therapy (HAART), a combination of at least three drugs that typically includes either a protease inhibitor (PI) or a non-nucleoside analogue reverse transcriptase inhibitor (NNRTI) and two nucleoside analogue reverse transcriptase inhibitors (NRTIs), has substantially improved the prognosis of HIV-infected patients who have access to these drugs in industrialised countries.[1-3]

In resource-poor settings in Africa, Asia and Latin America, where 90% of people with HIV/AIDS live, access to antiretroviral therapy is limited to a small minority of patients, due to the high cost of drugs and the lack of an infrastructure capable of delivering the therapy in poor countries. In recent years, costs of proprietary drugs have fallen and generic preparations have become available. More recently, many African countries have qualified for grants from the "Global Fund to fight AIDS, Tuberculosis and Malaria". Worldwide, the Fund has approved over one billion US dollars for programmes against HIV/AIDS.[4] On World AIDS Day (December 1, 2003) WHO launched the '3 by 5' initiative (3 million patients treated by 2005), whose strategy involves simplified, standardized tools for delivering and monitoring antiretroviral therapy.[5] The American "President's Emergency Plan for AIDS Relief" intends to give 2 million people access to ART.[6] The government of South Africa, one of the countries hardest hit by the AIDS epidemic, has recently set up an "Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment" to make antiretrovirals widely available in the public health system.

These developments clearly demonstrate that the debate on HAART in developing countries has moved from the question whether the introduction of HAART is cost-effective in the light of competing priorities and fragile health systems[7,8] to questions of how effective potent antiretroviral therapy will be in these settings.[9,10] There is widespread agreement that research and evaluation efforts are needed, so that epidemiological and clinical data can be collected and the programmes can be modified and improved over time.[5,6]

Objectives

UNAIDS organized a workshop on 2 to 4 December 2003 in Lisbon, Portugal, in order to review estimates of HIV-positive persons who are in need of treatment. The present document was prepared following this workshop and aims to contribute to:

1) Quantifying the time period among adults between eligibility for antiretroviral treatment and death, in the absence of antiretroviral therapy (ART), with a focus on low- and middle income countries, based on a literature review. Eligibility for antiretroviral treatment should be based on the recent WHO recommendations: WHO stage IV (clinical AIDS), regardless of the CD4 count;
WHO stages I, II or III with a CD4 count below 200 cells per μL; WHO stages II or III of HIV disease with total lymphocyte count below 1200 cells per μL.

2) Exploring factors that are associated with differences in the time period between eligibility for antiretroviral treatment and death, and quantify this time period according to important modifying factors. Non-treatment factors might include age, geographic area, gender, mode of transmission, HIV subtype, etc. Treatment factors include care, prophylaxis for opportunistic infections, and other non-ART treatments.

3) Exploring differences in the time period between eligibility for antiretroviral treatment and death, between low- and middle income countries, and high-income countries in the pre-ART era.

4) Estimating the time from seroconversion to the point when people become eligible for treatment (AIDS, less than 200 CD4 cells /μL, less than 1200 lymphocytes/μL) in developing countries.

5) Estimating the time from seroconversion to when people are eligible for treatment (AIDS, less than 200 CD4 cells/μL, less than 1200 lymphocytes/μL) in industrialised countries before the advent of ART.

Methods

A literature search was performed in Medline and Embase. The search covered the period from 1990 to November 2003 and used search terms 'AIDS', 'HIV infections', 'disease progression', and 'mortality'. The reference lists of relevant original papers and review articles were also scrutinized. Because of time constraints, conference abstracts were not considered. One of us (MS) extracted information on mean survival after seroconversion, time to onset of AIDS, and time to less than 200 CD4 cells/μL or < 1200 lymphocytes/μL. In various reports, this information had to be estimated from Kaplan-Meier curves or calculated from estimates at 1, 2 or 5 years reported in tables. We estimated median survival time from these figures assuming a constant hazard function λ, as follows:

$T_{med} = - \ln 2 / \lambda$

We used reported incidence rates (number of events per 100 person-years of observation) to estimate λ, which then allowed the calculation of median survival times, for example by CD4 cell strata.

We used data from published studies from Europe, North America and New Zealand from the pre-ART era and performed de novo analyses of the Swiss HIV Cohort study for comparisons of the survival experience between low and middle income and industrialised countries. The published studies were taken from an earlier review of survival time after AIDS in the pre-ART era[11]. The analyses of the Swiss cohort were based on patients with heterosexual or homosexual transmission and clinical progression before ART was introduced. All statistical analyses were done in the statistical package Stata (version 8.2, College Station, Texas, USA).

Results

We examined over 300 references of potentially relevant studies from resource-limited settings. Two-hundred and forty studies were found not to be relevant based on the abstract and 65 papers were ordered and examined in detail. Forty-six were excluded because outcomes were not relevant or crucial information was missing. Twenty studies were included in the review.

Time from AIDS to death

In resource-limited settings, eight studies[12-19] provided data on the time between the occurrence of first AIDS-defining events and death. Median survival after diagnosis of AIDS ranged

between 6 and 19 months. Study characteristics are summarised below:

Study, year of publication	N	Country	Years	Median survival (Tmed) and 95% CI [months]	Comments
Bégaud, 2003[12]	11	Central African Republic	1995-2000	6.5 (2.5 - 16)	
Hira, 2003[13]	54	Mumbai, India	1994-2000	19	25% with TB
Menesia, 2001[14]	1231	Riberão Preto, Brazil	1986-1997	10.3	10 months in 1991-1995; 28 months in 1996-1997
Post, 2001[15]	280	Cape Town, South Africa	1984-1997	11.5	Median CD4 count of 111
French, 1999[16]	56	Entebbe, Uganda	before 1998	6	
Fonesca, 1999[20]	48	São Paolo, Brazil	1987-1995	19	AIDS, some patients on ART
Morgan, 1997 & 2002[18,21]	44	Rural area, Uganda,	1990-2000	9.3 (3.4 - 16.6)	
Kitayaporn, 1996[19]	329	Hospital in Bangkok, Thailand	1987-1993	7	Median total lymphocyte count 904; 30% mortality in first month

For comparison, six studies of clinical progression [22-27] that were conducted in industrialised countries before the introduction of combination therapy found mean survival rates after onset of AIDS between 9.5 and 22 months:

Study, year of publication	N	Country	Years	Median survival (Tmed) and 95% CI [months]	Comments
Rothenberg, 1987[22]	5833	New York City, USA	1981-85	11.5	First AIDS definition; 11% died at AIDS diagnosis
Lemp, 1990[23]	4323	San Francisco, USA	1981 1987	10.1 15.6	Survival longer for KS Improvements over time with PCP as AIDS defining disease
Pedersen, 1990[24]	231	Denmark	1981-89	13 (11-16)	
Friedland, 1991[25]	526	New York City, Bronx	1981-87	9.5	Differences by initial illness
Bindels, 1991[26]	515	Amsterdam	1986 1988	14 22	Overall 16 months
Carlson, 1991[27]	191	New Zealand	1981-89	14	

Survival from < 200 CD4 lymphocytes per mm^3 to death

A CD4 lymphocyte count below 200 cells per mm^3 is an important risk factor for clinical progression, indicating that antiretroviral treatment should be started without delay. Five

reports[16,28-31] provided information on the time between a CD4 cell count below 200 cells and death. Unfortunately, the exact number of CD4 lymphocytes was rarely reported. Survival ranged between 7 and 38 months, and survival was longer for patients who received some antiretroviral therapy:

Study, year of publication	N	Country	Years	Median survival (Tmed) and 95% CI [months]	Comments
Pathipvanich, 2003[28]	422	Lampang province, Thailand	1995-1999	10.8 (na)	82% < 100 CD4 cells, partially treated
Pathipvanich, 2003[28]		Lampang province, Thailand	1995-1999	38 (28 - 62)	100-199 CD4 cells, partially treated
Kumarasamy, 2003	71	Chennai, southern India	1996-2000	33	46 months with ART
Schim van der Loeff,[29] 2002	378	Fajara in The Gambia	1986-1997	7 (5 - 9)	
Kilmarx, 2000[30]	15	Northern Thailand	1991-1998	11 (7 - 15)	96% subtype E
French, 1999[16]	78	Semi-rural Entebbe, Uganda	before 1998	9 (7 - 15)	

In industrialised countries, two American[32,33] studies estimated survival after CD4 cell counts had declined to below 200 CD4 lymphocytes per mm^3:

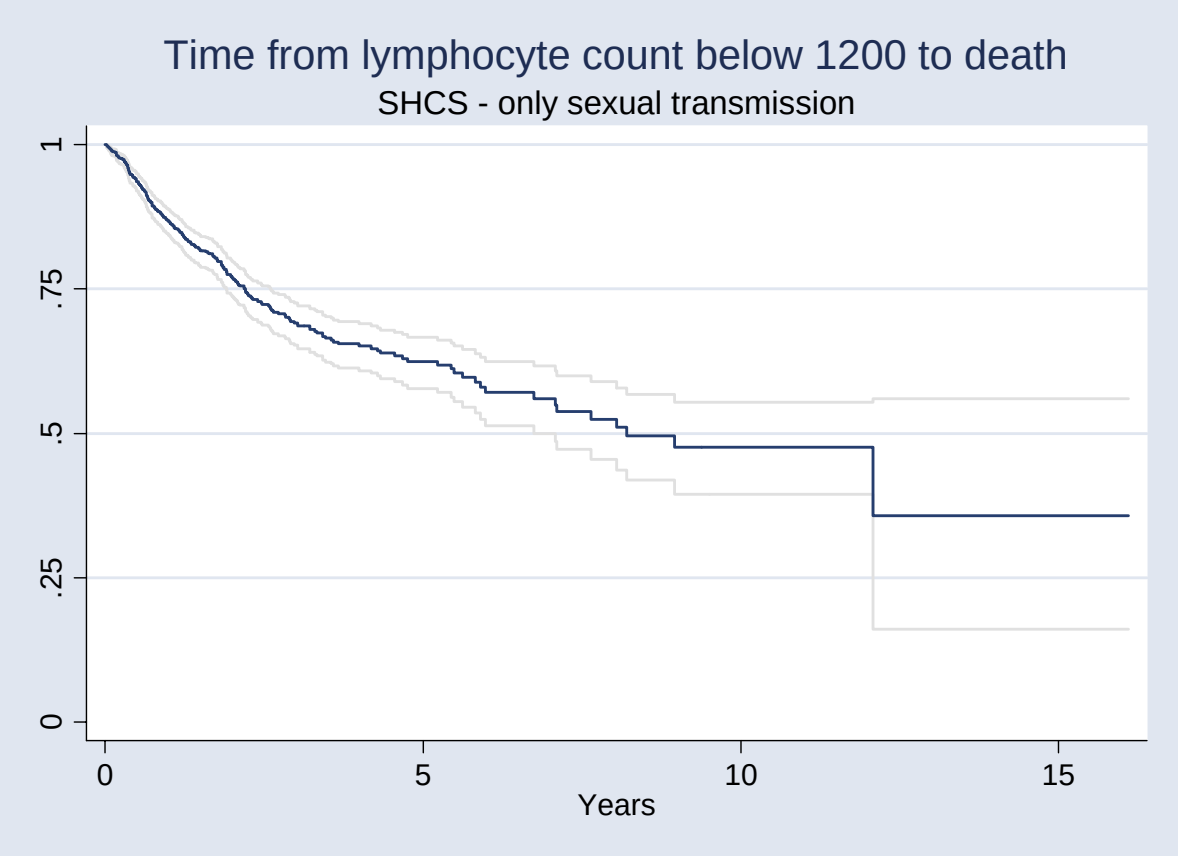
Study, year of publication	N	Country	Years	Median survival (Tmed) and 95% CI [months]	Comments
Osmond, 1994[33]	180	San Francisco, USA	before 1986 1986-88	28 40	Homosexual men with AIDS
Hanson, 1993[32]	156 117	Atlanta, USA	before 1991	11 - 13 36 - 41	AIDS No AIDS

The level of CD4 lymphocytes per mm^3 clearly affects survival. Three studies[16,29,30] reported median survival times for patients with CD4 cell counts in the range of 200 to 500 cells per mm^3.

Study	Population, Country, Years	Median survival (Tmed) and 95% CI [months]	CD4 interval	Issues
Kilmarx, 2000[30]	88 Northern Thailand, 1991-1998	91 (63 –131)	200-500	96% HIV-subtype E
French, 1999[16]	Uganda, before 1998	48	200-499	
Schim van der Loeff,[29] 2002	Gambia, 1986-1997 (N=303)	40 (33 –51)	200-499	

Survival after a total lymphocyte count below 1200/mm^3

Our search did not identify any relevant published data. We performed an analysis of Swiss HIV Cohort Study (SHCS) data, restricting observation time to the period before antiretroviral treatment became available. Individuals were censored at the time they started any type of antiretroviral treatment. We measured time from the first laboratory examination with a total lymphocyte count between 700 and 1200 per mm^3. Only individuals with presumed heterosexual or homosexual transmission were included. The Kaplan-Meier plot is shown below. The SHCS data become scarce after 5 years, but indicate that median survival is longer than 5 years:



Brief review of factors associated with longer or shorter survival

Age

Various studies, both from developing[18] and from industrialised countries[34], have shown that young age is associated with longer survival, independently of the mode of HIV transmission.

Sex

Sex does not seem to be associated with survival. In developing countries, women are infected at younger age; sex may thus act as a confounder. Pregnancy does not appear to materially affect clinical progression.

Cohort effects

In industrialised countries, cohorts infected in the late 1980 have longer survival than those with

earlier seroconversion, probably due to the gain in doctors' expertise and improvements in the overall medical management of these patients[24]. The wider use of prophylaxis against opportunistic infections will also have contributed to increasing survival.

Immunological and virological parameters

As in the industrialised world, low CD4 lymphocytes[20] and high viral load[30] are associated with faster disease progression in resource-poor countries.

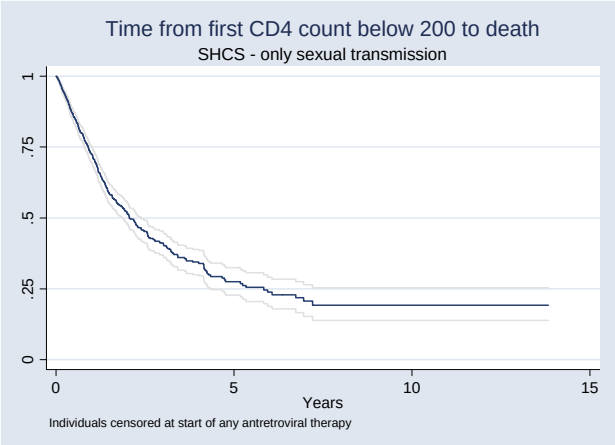
Type of virus

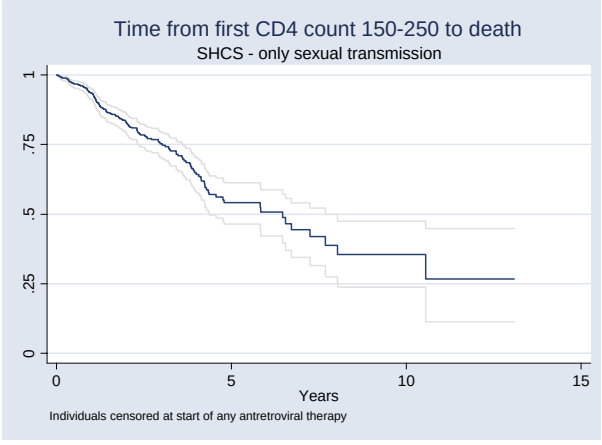
HIV-2 is less virulent than HIV-1. Patients infected with HIV-2 progress slower[29,35,36]. The role, if any, of HIV-1 subtypes is less clear. Subtype D may lead to faster progression[37]; subtype A may be associated with slower progression[38].

Summary and conclusions

Survival after AIDS-defining events or specified CD4 lymphocytes levels tends to be shorter in developing than in industrialised countries. In developing countries, estimates of median survival after AIDS scatter around 1 year. Similar results are obtained for survival after CD4 cell counts have dropped below 200 cells per mm^3, but estimates are more heterogeneous.

The latter results will be influenced by the exact distribution of CD4 cell counts among patients with less than 200 cells. This is illustrated by the following analyses of the SHCS data described above: In the first analysis we measured time from the first CD4 cell count below 200 cells per mm^3. The median CD4 count in this situation was 100 cells per mm^3. In the second analysis we selected patients with CD4 cell counts between 250 and 150 cells per mm^3, resulting in a median count of 200 cells per mm^3. The Kaplan-Meier plots show that the observed median survival time differs substantially between these two patient groups. We acknowledge that these results may be biased due to the fact that follow-up was censored at the time of starting anti-retroviral treatment, which means that slow progressors will tend to be overrepresented. Furthermore, some patient will have received prophylactic treatment to prevent AIDS defining complications. The results nevertheless illustrate the crucial importance of the CD4 cell count at time 0.





The table below compares the survival data obtained from our review of the literature from resource-poor settings with the results of the analyses of Swiss HIV Cohort Study data:

Time measured from	Published studies from resource-poor settings (median, range)	Estimates from the Swiss HIV Cohort Study (SHCS) (median, 95% CI)
AIDS	11 (7- 19)	17.6 (15.9 – 19.0)
CD4 count <200	11 (7 - 38)	24 (22 – 29) *
CD4 count 150 to <250	not available	77 (52 – 92) **

* median CD4 cell count at time 0: 100 cells per mm3

** median CD4 cell count at time 0: 200 cells per mm3

The analyses of SHCS data included patients with sexual transmission of HIV only. Follow up related to person-time of observation in the calendar years before 1996 and was censored when starting any type of anti-retroviral treatment.

The SHCS data indicate that survival was 3.2 times longer (77/24 months) in the group of patients with a median CD4 cell count of 200 cells per mm^3 than in the group with a count below 200 cells per mm^3 (median count of 100 cells per mm^3). Assuming that this ratio also holds for resource-poor settings, survival for individuals having reached a count of 200 CD4 cells per mm^3 would be estimated at 2.9 years (3.2 x 11 months). We stress that this estimate is associated with substantial uncertainty. Also, it is clear that at present CD4 cell counts in patients attending treatment facilities in the South have often dropped substantially below 200 cells per mm^3.

Our review has several limitations. The literature search was restricted to published studies and did not include conference abstracts, grey literature or unpublished material. It seems unlikely, however, that the inclusion of studies reported as abstracts only or unpublished studies would have materially changed our conclusions.

The type of data reported on survival was heterogeneous, confirming earlier observations on common difficulties with systematic reviews of prognostic studies.[39] Indeed, the studies reviewed here presented data in various ways, as median survival, Kaplan-Meier curves, estimates of survival at 1, 2 or 5 years or as incidence rates (events per person-years of observation). This meant that the required information sometimes had to be extracted from graphs or estimates of median survival time had to be calculated from rates, which may have introduced both systematic and random error. Furthermore, definitions of AIDS and categories of CD4 lymphocytes varied, studies sometimes included patients both prospectively and retrospectively, and a few studies included patients on antiretroviral monotherapy. This meant that a formal meta-analysis could not be performed. A collaborative individual-patient-data analysis is required to overcome these limitations. The data presented here may nevertheless represent the best available information, which should be used in the spirit of sensitivity analysis when estimating the number of HIV-infected people in need of potent antiretroviral treatment in low income countries.

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Appendix: Overview of studies on survival after AIDS in industrialised countries before the advent of HAART.

Population based studies analyzing survival trends of AIDS patients			
Authors	Year published	Population	Results / Comment
Rogers, et al [1]	1997	AIDS cases reported in United Kingdom Diagnosed through 12/31/91 Follow-up through 4/30/94 N=5,796	Stable median survival (19.4 months - 20.3 months) from 1988 to 1991
Luo, et al [2]	1995	AIDS cases reported in Australia Diagnosed through 11/1/91 Follow-up through 3/31/94 N=3,204	Decrease in 1 year survival from 1988 (66.6%) to 1991 (54.7)
Turner, et al [3]	1995	AIDS cases reported to the New York State AIDS Diagnosed from 1985 to 1990 N=5,584 adult cases N=734 children	Median survival was 62 months for all children compared with 11 months for adults
Zangerle, et al [4]	1995	AIDS cases reported to the Austrian Health authorities Diagnosed through 12/31/92 Follow-up through January 94 N=901	Slight decrease in 1 year survival from 1988 (62%) to 1991 (58%)
Blum, et al [5]	1994	AIDS cases reported to the New York City Department of Health Diagnosed through June 89 Follow-up through 12/1/90 N=20,760	Note that “zero” survivors excluded from the analysis (persons who died during the same month in which they were diagnosed with AIDS)
Maden, et al [6]	1993	AIDS cases diagnosed in Washington state (US) Diagnosed through December 89 Follow-up through October 91 N=1,136	For time trends only 1,136 cases meeting the 1985 AIDS definition were analyzed (slight decrease from 1988 to 1989)
Tu, et al. [7]	1993	AIDS cases reported to the Centers for Disease Control Diagnosed from 1983 to first	Median survival for AIDS cases with PCP increased from 7

Population based studies analyzing survival trends of AIDS patients			
Authors	Year published	Population	Results / Comment
		quarter 1991 N approx. 90'000	months to approx. 15 months
Whitmore-Overton, et al [8]	1993	AIDS cases reported in United Kingdom Diagnosed through 9/30/90 Follow-up through 12/31/91 N=3,984	Overall median survival was longer for cases diagnosed 1987 and later (19 months) than cases for cases diagnosed before 1987 (10 months)
Seage III GR, et al [9]	1993	AIDS cases reported in Massachusetts Diagnosed 1/1/79 to 12/31/88 Follow-up through 12/31/89 N=1,931	Overall 1 year survival increased between ≤1984 (31%) and 1988 (60%)
Holman RC, et al [10]	1992	AIDS cases in hemophiliac men reported to CDC Diagnosed 1/1/81 to 6/30/90 Follow-up 6/30/90 N=1,514	Hemophiliac with other HIV risk are compared to those without such risks observing only marginal differences in survival
Lemp GF, et al [11]	1992	AIDS cases reported in San Francisco Date of diagnosis 7/81 to 12/31/90 Follow-up through 5/15/91 N=7,045	Women had shorter median survival (11.1 months) than men (14.6 months): use of therapies is suspected to be differing
Moore RD, et al [12]	1991	AIDS cases reported to Maryland Human Immunodeficiency Virus Information System, USA Diagnosed 1/83 to 6/89 Follow-up through 6/90 N=1,028	1 year survival increased between 1985 (47%) and 1989 (56%), also 1 year survival from 1985 (23%) to 1989 (35%)
Piette J, et al [13]	1991	AIDS cases reported to CDC Date of diagnosis 1/1/84 to 12/31/86 Follow-up through 9/89 N=23,271	Main focus on regional differences
Lafferty WE, et al [14]	1991	AIDS cases reported to Washington State, USA	Median survival increased from 11.3

Population based studies analyzing survival trends of AIDS patients			
Authors	Year published	Population	Results / Comment
		Diagnosed through 12/87 Follow-up through 12/88 N=609	months (≤1985) to 20.8 months (1987)
Bindels PJ, et al [15]	1991	AIDS patients diagnosed in Amsterdam, Netherlands and reported to municipal health service Diagnosed through 12/31/88 Follow-up through 4/90 N=515	Median survival increased between 1985 (9 months) and 1988 (22 months)
Carlson RV, et al [16]	1991	AIDS cases reported in New Zealand Reported through 6/30/90 Follow-up not stated N=179	Median survival of 58 weeks
Harris JE [17]	1990	AIDS cases reported to CDC Diagnosed 1/84 to 9/87, only pre87 Def Follow-up to 7/30/88 N=36,847	One year survival increased between 1984 (43%) and 1987 (55%). No improvement in survival for cases with PCP
Lemp GF, et al [18]	1990	AIDS cases reported in San Francisco Diagnosed 7/81 to 12/31/87 Follow-up through 12/31/88 N=4,323	Overall median survival increased between 1981 (10.1 months) and 1987 (15.6 months), but decreased for cases with Kaposi's sarcoma
Payne SF, et al [19]	1990	AIDS cases diagnosed with Kaposi's Sarcoma and reported to the San Francisco Department of Public Health surveillance system through 12/31/1987 Follow-up through 21/31/1988 N=1,015	Year of diagnosis significantly associated in multivariate analysis (continuously improving between 1981 and 1987)
Pedersen C, et al [20]	1990	Adult AIDS patients reported to Danish Health Authorities Reported through 1/1/88 Follow-up through 8/1/89 N=231	Small number of cases; survival after PCP increased but not for cases with other AIDS defining illnesses

Population based studies analyzing survival trends of AIDS patients			
Authors	Year published	Population	Results / Comment
Solomom PJ, et al [21]	1990	AIDS cases reported in Australia Diagnosed prior to 12/31/88 Follow-up through 12/31/88 N=1,187	Improved survival after August 1987 compared to cases diagnosed before that (survival modeled as exponential distribution)
Whyte BM, et al [22]	1989	AIDS cases reported in Australia Diagnosed prior to 7/31/87 Follow-up through 7/31/87 N=561	Longest median survival for cases with KS (12.4 months) and shortest for cases with lymphoma (7.0 months)
Bacchetti P, et al [23]	1988	AIDS cases reported to the San Francisco Department of Public Health surveillance system through May 1984 Follow-up 12/31/85 N=505	Cases exclusively according to pre 1985 AIDS definition
Reeves GK, et al [24]	1988	AIDS cases reported in United Kingdom to the Communicable Diseases Surveillance Centre (CDSC) Diagnosed prior to 3/31/87 Follow-up through 9/30/87 N=663	A preliminary analysis, no time trends
Rothenberg R, et al [25]	1987	AIDS cases reported in New York City Diagnosed mid 81 to 12/31/85 Follow-up not clearly stated N=5,833	Overall increase in 1 year survival between 1981 (42%) and 1985 (50%)
Marasca G, et al [26]	1986	AIDS cases reported in United Kingdom to CDSC Reported through 6/1/85 Follow-up not stated N=178	Median survival was 21 months for cases with KS and 13 months for cases with PCP

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