
Independent epidemics of heterosexual and homosexual HIV infection in South Africa—survival differences

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Summary

Survival with HIV infection is shorter in sub-Saharan Africa than in developed countries. The pattern of HIV transmission in our region has changed from homosexual to heterosexual, with viral subtypes similar to those in North America/Europe and Central Africa, respectively. We compared survival for the two transmission patterns after AIDS, and after the first CD4+ lymphocyte counts <200/μl and <50/μl, for adults presenting 1988–1993. Anti-retroviral therapy was excluded. There were 180 homosexuals (63% White, 56% employed) and 314 heterosexuals (67% Black, 34% employed). Extrapulmonary tuberculosis was the AIDS-defining

diagnosis in 36/90 heterosexuals and 5/58 homosexuals ($p < 0.0001$). Survival after AIDS was longer in heterosexuals ($p = 0.0015$), but AIDS occurred earlier as shown by their higher CD4+ count at AIDS onset (median 98/μl vs. 40/μl; $p = 0.036$). Survival was similar in the two groups after first CD4+ count <200/μl and <50/μl. Race, socioeconomic status and morbidity are markedly different in the two transmission groups. AIDS occurs with less severe immune suppression in heterosexuals, with correspondingly longer survival. Survival after defined CD4+ counts, however, is remarkably similar.

Introduction

The prognosis of HIV infection in sub-Saharan Africa has been reported to be worse than in industrialized countries.^{1,2} This may be due to death from endemic non-opportunistic infections (particularly *Mycobacterium tuberculosis*, the salmonellae, and *Streptococcus pneumoniae*) prior to the onset of severe immunosuppression.¹ This seems plausible given the overburdened and poorly-funded health-care facilities in most countries in this region. Death prior to the onset of severe immunosuppression may also explain the observed scarcity of many opportunistic infections in HIV-infected patients in Africa.^{1,3}

Alternatively, the poorer prognosis in Africa may be due to more rapid disease progression as a result of more virulent HIV subtypes, genetic predisposition, or the presence of co-factors. Supporting this hypothesis, the Nairobi sex-worker cohort study reported

progression to AIDS twice as rapid as that in cohorts from industrialized countries.⁴

The transmission pattern of HIV in our area has changed from an initial homosexual/bisexual epidemic (pattern 1) to a heterosexual epidemic (pattern 2). Our pattern 1 patients have viral subtype B (the same as in North America/Europe), whilst pattern 2 patients have subtype C, which occurs in sub-Saharan Africa,⁵ indicating that the two epidemics are independent. Health-care facilities in South Africa are better than elsewhere in sub-Saharan Africa,⁶ which enables us to diagnose and treat most opportunistic infections, and monitor serial CD4+ lymphocyte counts. However, anti-retroviral therapy is not generally available in the state health sector. We are thus in a unique position to compare the outcome of the two transmission patterns in an HIV-infected population unexposed to anti-retroviral therapy.

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Methods

Somerset and Groote Schuur hospital HIV clinics are both affiliated to the University of Cape Town. The same treatment protocol is used at both clinics, and medical personnel are partly shared. Patients were referred from primary care, often following screening for insurance or blood donation, or from hospitals in the Western Cape region. There was no private specialist HIV care available. Adult patients attending for their initial visits between 1988–1993 were studied. All patients had HIV-1 infection confirmed by ELISA and Western blot or three different ELISAs on specimens drawn on two occasions. Data were acquired by retrospective chart review prior to December 1991, and prospectively thereafter. Follow-up continued until April 1995. CD4+ lymphocyte counts were performed 3- to 6-monthly by flow cytometry. Demographic data, including sexual preferences and employment status, were collected. Patients who were taking anti-retroviral therapy were excluded. Cotrimoxazole primary prophylaxis was routinely prescribed from 1991 for patients with CD4+ counts <200/ μ l. Primary prophylaxis for fungal or mycobacterial infections was not used.

Date of death was obtained from hospital records or from deaths reported to the clinics by relatives or friends. In addition, regional death records were searched if patients failed to attend for more than 6 months.

Statistical analysis was done using the software packages EpiInfo version 6 (Centers for Disease Control), SAS and Statgraphics version 6 (Statistical Graphics). Survival from the first AIDS diagnosis (1987 Centers for Disease Control case definition)⁷ and the first recorded CD4+ lymphocyte counts <200/ μ l and <50/ μ l were assessed by Kaplan-Meier analysis. Patients were right censored if their last clinic attendance was before 2 years follow-up. The survival curves for patterns 1 and 2 were compared using log rank tests. Yates' correction was applied to χ^2 tests.

Results

The transmission pattern changed from predominant homosexual transmission to heterosexual transmission during the study period (Figure 1). There were 662 patients whose first clinic visit was between 1988 and 1993. Anti-retroviral therapy was taken at some stage by 112 patients, and sexual preference was not recorded in 56, leaving 494 evaluable patients (36% pattern 1, 64% pattern 2). Demographic data is shown in Table 1. Pattern 2 patients were significantly younger ($p < 0.01$). There

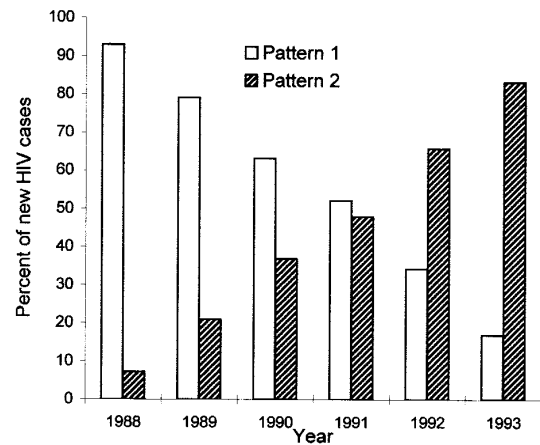


Figure 1. The proportion of new pattern 1 and 2 patients attending the HIV clinics in Cape Town from 1988 to 1993.

Table 1 Demographic data

	Pattern 1	Pattern 2
<i>Race</i>		
White	114 (63.3%)	11 (3.5%)
'Mixed'	65 (36.1%)	93 (29.5%)
Black	1 (0.6%)	210 (67%)
Age (years)	33.1 \pm 8.95	30.22 \pm 8.94
Males	180 (100%)	147 (46.8%)
Employed*	101 (56.1%)	50 (34%)

*Employment status applies only to males.

were no intravenous drug users. Employment status was assessed only for males. Because being unemployed at the time of presentation may reflect disability due to HIV, we also evaluated prior employment status. The proportion of males who had ever worked was 70.6% in pattern 1 compared with 47.5% in pattern 2 ($p < 0.0001$). In those patients who had ever worked, unskilled or semi-skilled labour was performed by 18% of pattern 1 patients compared with 73.5% of pattern 2 patients ($p < 0.0001$).

Nine patients in each transmission pattern died prior to the onset of AIDS ($p = 0.308$). The degree of immunosuppression in each group was similar as assessed by CD4+ lymphocyte count at first visit (357 \pm 244 pattern 1; 312 \pm 221 pattern 2; $p > 0.05$) and the proportion with AIDS at first visit (13% pattern 1; 17% pattern 2; $p = 0.18$). The mean time to developing AIDS was also similar (12.3 months pattern 1; 11.3 months pattern 2; $p > 0.05$). Medical care was similar, as assessed by the number of clinic visits per year prior to developing AIDS (6.3 visits pattern 1; 5.5 visits pattern 2; $p > 0.05$).

AIDS was diagnosed on entry or subsequently occurred in 148 patients (58 pattern 1, 90 pattern 2). The commonest AIDS-defining conditions are listed in Table 2. *Pneumocystis carinii* pneumonia

Table 2 Most frequent AIDS-defining diagnoses in the two transmission patterns

AIDS-defining condition	Pattern 2 (n=90)	Pattern 1 (n=58)	Odds ratio (95% CI)
Extrapulmonary TB	36 (40%)	5 (9%)	7.07 (2.47–24.56)
<i>Pneumocystis carinii</i>	6 (7%)	11 (19%)	0.31 (0.09–0.98)
Kaposi's sarcoma	8 (9%)	8 (14%)	0.61 (0.19–2.0)
Candidosis	10 (11%)	5 (9%)	1.33 (0.39–5.22)
Herpes simplex	7 (8%)	6 (10%)	0.73 (0.2–2.8)
Wasting syndrome	5 (6%)	7 (12%)	0.43 (0.1–1.67)

TB, tuberculosis.

occurred more frequently in pattern 1 patients ($p=0.043$) whilst extrapulmonary tuberculosis occurred more frequently in pattern 2 patients ($p<0.0001$). CD4+ lymphocyte counts at the time of AIDS-defining diagnosis were available in 53 patients. These were lower in pattern 1 patients (median 40/ μ l; interquartile range 16–126) compared with pattern 2 patients (median 98/ μ l; interquartile range 47–194; $p=0.036$, Mann-Whitney U test). Pattern 2 patients survived significantly longer ($p=0.0015$)

following AIDS diagnosis (evaluable in 130 patients)(Figure 2).

Survival from the first recorded CD4+ lymphocyte count $<200/\mu$ l ($n=190$) and $<50/\mu$ l ($n=82$) was similar for both patterns (Figure 3). Survival from the first CD4+ lymphocyte count $<200/\mu$ l was similar for male and female pattern 2 patients ($p=0.33$). Controlling for age by Cox proportional hazard in males with CD4+ lymphocyte count $<200/\mu$ l showed no significant difference in survival (risk ratio for death in pattern 1 patients 1.857, 95% CI 0.975–3.537; $p=0.06$). In this group, survival was shorter for pattern 1 compared with male pattern 2 patients <33 years ($p=0.018$) but similar for males 33 years or older ($p=0.55$) (a cutpoint of 33 years was chosen because it gave approximately equal numbers in the sexual preference groups). We also controlled for the time when AIDS or the first CD4+ count $<200/\mu$ l or $<50/\mu$ l was found, as the quality of care may have changed over time. This did not alter the findings that pattern 2 patients survived longer after AIDS and that survival was similar after first CD4+ count $<200/\mu$ l or $<50/\mu$ l.

Discussion

The major finding of our study was that survival, when assessed from CD4+ counts $<200/\mu$ l and $<50/\mu$ l, was similar for both major transmission

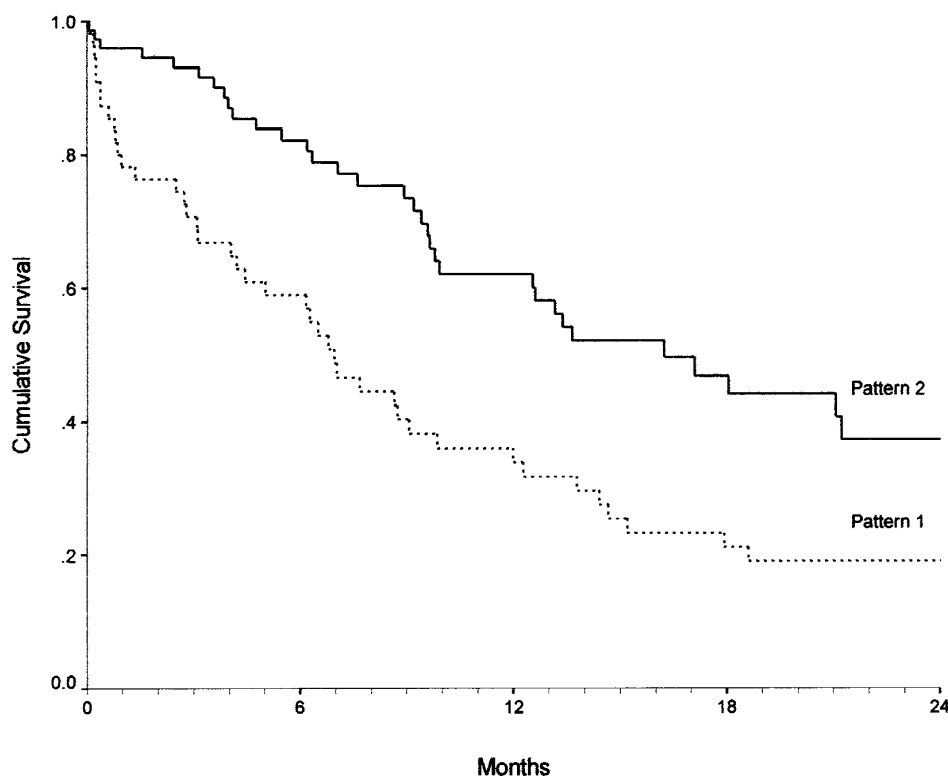


Figure 2. Cumulative survival after the first AIDS diagnosis. Survival was longer in pattern 2 patients ($p=0.0015$).

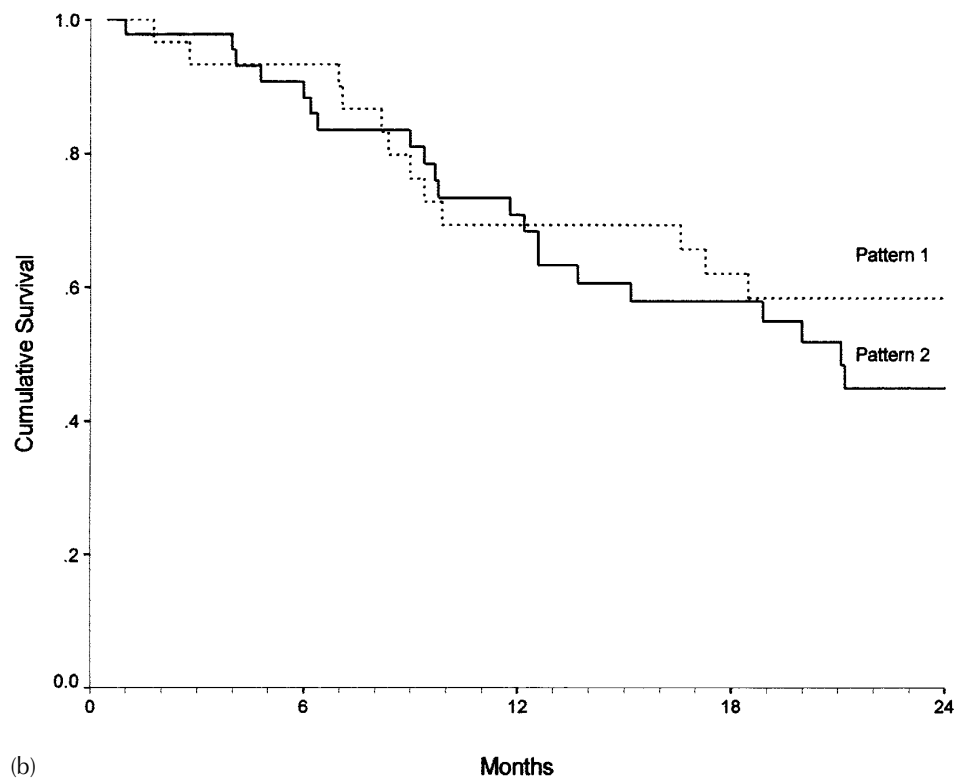
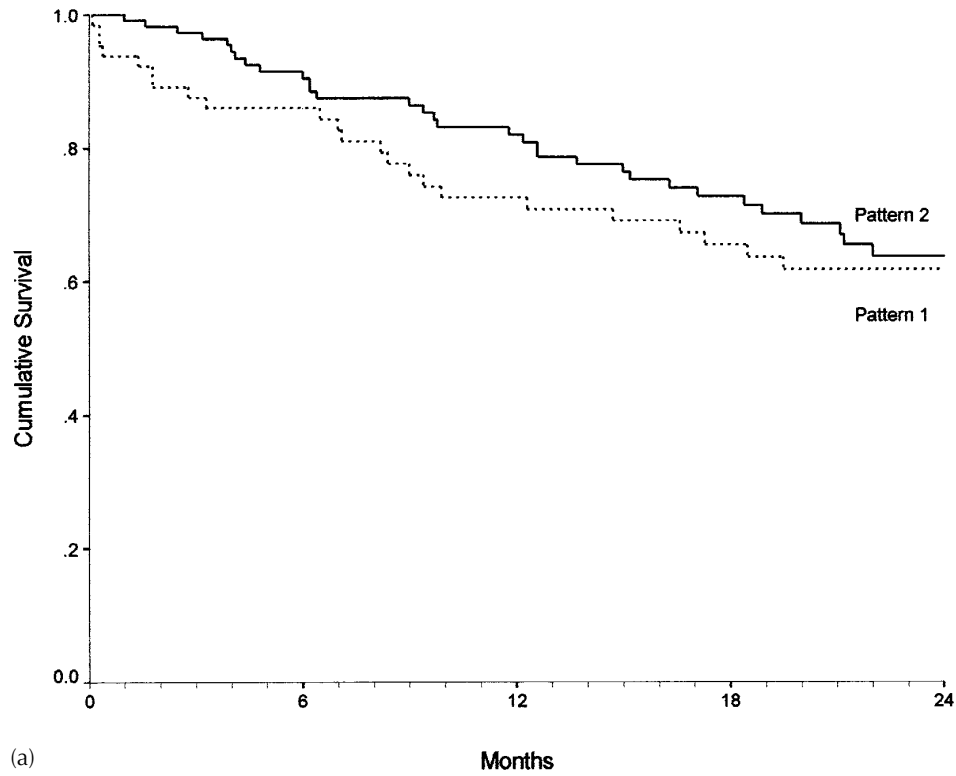


Figure 3. Cumulative survival following CD4⁺ lymphocyte counts **a** <math>< 200/\mu\text{l}</math> and **b** <math>< 50/\mu\text{l}</math>. Survival was similar for pattern 1 and 2 patients (**a** $p=0.206$; **b** $p=0.91$).

patterns. This was not due to age differences, which are important prognostically,⁸ between the two groups. Although our observations were largely con-

fined to late HIV disease, the fact that there were no excess deaths in pattern 2 patients before AIDS provides further support to our finding that disease

progression is similar for both transmission patterns. The longer survival of pattern 2 AIDS patients is reflected in their higher frequency of extrapulmonary tuberculosis. This presents with higher CD4 + lymphocyte counts than most other AIDS-defining conditions, and is associated with longer survival.⁹

The CDCs expanded definition of AIDS¹⁰ has been criticized by one centre, which found that the revised definition led to a threefold increase in patients defined as having AIDS, and their survival was more than twice as long.¹¹ The use of a CD4 + lymphocyte <200/ μ l to define AIDS is problematic, because of considerable differences in results from different laboratories.¹² These problems apply to industrialized countries—resource-poor countries are generally unable to afford CD4 + lymphocyte determinations. In addition, the inclusion of pulmonary tuberculosis as an AIDS-defining condition is not applicable to areas where tuberculosis is endemic.¹³ Therefore we used the 1987 CDC case definition of AIDS.⁷

In sub-Saharan Africa, the reason for the scarcity of certain major opportunistic infections is thought to be due to death before the development of severe immunosuppression.^{1,3} In our pattern 2 patients, tuberculosis continued to predominate, even with severe immunosuppression. Tuberculosis is endemic in the African and mixed race communities in our area.¹⁴ We do see the major opportunistic infections in our pattern 2 patients, with the notable exception of *Mycobacterium avium* complex infection, although this occurs in our environment.¹⁵ Geographical differences in the incidence of these infections may be due to the protective effect of BCG vaccination,^{16,17} which the majority of patients of all races in Cape Town have received.¹⁴

Shorter survival has been reported for HIV-infected patients with lower socioeconomic circumstances.¹⁸ Socioeconomic status, as assessed by current or previous employment status, was markedly lower in our pattern 2 patients. Despite this, their survival was similar to pattern 1 patients. The likely explanation for this is that patients were treated with the same quality of care. This view is supported by a recent American study from a single centre which also found that socioeconomic status was not a determinant of outcome.¹⁹

Our pattern 2 patients are similar to those elsewhere in sub-Saharan Africa in terms of their morbidity (predominantly tuberculosis and non-opportunistic bacterial infections²⁰) and their HIV-1 viral subtype.⁵ The shorter survival in HIV-infected patients observed elsewhere in Africa is thought to be largely due to death from non-opportunistic infections because of poor access to inadequate health care.¹ The fact that survival is similar for both transmission patterns in Cape Town is presumably due to our better health-care resources,⁶ which

enables us to investigate and treat most HIV-related infections. This is illustrated by the similar survival of our AIDS patients to those in Europe⁹ and New York.²¹ Our patients with severe immune suppression (a CD4 + lymphocyte count <50/ μ l) have a median survival similar to that reported from the USA.²² It is noteworthy that this similar survival in late HIV disease was achieved without anti-retroviral therapy.

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CD4+ lymphocyte count < 50/ μ l. *J Infect Dis* 1995; **171**:829–36.

Appendix

Life tables of survival analysis—numbers refer to evaluable patients or the number who died.

Appendix to Figure 2—survival after AIDS

	0	6	12	18	24	Deaths
	months months months months months					
Pattern 1	55	30	17	10	7	41
Pattern 2	75	50	31	17	8	35

Appendix to Figure 3a—survival after CD4 < 200

	0	6	12	18	24	Deaths
	months months months months months					
Pattern 1	67	54	42	36	31	23
Pattern 2	123	91	74	55	37	32

Appendix to Figure 3b—survival after CD4 < 50

	0	6	12	18	24	Deaths
	months months months months months					
Pattern 1	33	29	20	16	15	13
Pattern 2	49	39	29	20	12	22