References

1. UNAIDS. *Report on the Global HIV/AIDS Epidemic.* Geneva: June 2000.

2. Connor EM, Sperling RS, Gelber R, *et al.* Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med* 1994; **331**: 1173-1180.

3. Lindegren ML, Byers RH, Thomas P, *et al.* Trends in perinatal transmission of HIV/AIDS in the United States. *JAMA* 1999; **282**: 531-538.

4. Centers for Disease Control and Prevention. Administration of zidovudine during late pregnancy and delivery to prevent perinatal HIV transmission — Thailand 1996-1998. *MMWR* 1998; **47**: 151-154.

5. Moodley D. The SAINT Trial: Nevirapine versus zidovudine + lamivudine in prevention of peripartum HIV transmission, University of Natal, 13th International AIDS Conference, Durban, 9 July 2000. Available at: http://www.iac2000.org/abdetail.asp?ID=LbOr2.

6. Guay LA, Musoke P, Fleming T, *et al.* Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* vol 354, Sept 4, 1999; **354:**

7. Saba J, on behalf of PETRA Trial Study Team. Interim analysis of early efficacy of three short ZDV/3TC combination regimens to prevent mother to child transmission of HIV-1. The PETRA trial. Abstract S7. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, January 31 - February 4 1999.

8. Department of Health. *Report of Annual Antenatal Survey 1999.* Pretoria: Department of National Health. 1999.

9. UNICEF/UNAIDS/WHO/UNFPA. African regional meeting on pilot projects for the prevention of mother-to-child transmission of HIV. Gaborone, Botswana. March, 2000. Available at: http://www.unaids.org/publications/documents/mtct/Gaborone meeting MTCT.doc. Accessed December 2000.

10. Mazhani L, Phiri L, Keapoletswe K, Bowelo M, Mugabe M, Mouzin E. Implementation of a population-based pilot program to reduce mother-to-child HIV transmission, Botswana. From: 13th International AIDS Conference, Durban, 9 July 2000. Available at: http://www.iac2000.org/abdetail.asp?ID=WeOrC550

11. Moyo S, Mhazo M, Mateta P, von Lieven A, Shetty AK, Hill DW, Basset MT. Acceptability of short-course ZDV prevention regimen by HIV infected pregnant women: should VCT in the antenatal setting be modified? From: 13th International AIDS Conference; July 9, 2000; Durban, South Africa. Available at: http://www.iac2000.org/abdetail.asp?ID=TuPpB1158

12. Kanshana S, Thewanda D, Teerarutkul A, Limpakarnjanarat K, Amornwichet P, Kullerk N, Mastro TD, Simonds RJ. Pilot program to implement short-course ZDV to reduce perinatal HIV transmission in Northeastern Thailand. From: 13th International AIDS Conference, Durban, 9 July 2000. Available at: http://www.iac2000.org/abdetail.asp?ID=WeOrC553

AIDS IN AFRICA — SURVIVAL ACCORDING TO AIDS-DEFINING ILLNESS

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Objective. Evaluation of prognostic significance of the type of AIDS-defining illness (ADI) and performance status in a cohort of AIDS patients.

Design, setting, subjects, outcome measures. A retrospective analysis of 280 patients with AIDS, as defined by the proposed World Health Organisation (WHO) clinical staging system, who attended two Cape Town-based HIV clinics between 1984 and 1997. Patients were stratified according to the type of initial ADI. Survival associated with each opportunistic event was determined by Kaplan-Meier analysis. Cox proportional hazard analysis was used to determine relative risk for death associated with three strata of ADI.

Results. Median survival associated with various initial ADIs varied from less than 3 months (encephalopathy and wasting), to over 2 years (extrapulmonary tuberculosis and herpes simplex virus infection). This effect of ADI on outcome was most striking in patients with relatively preserved CD4 counts (CD4 > 50/µl). A performance status score 4 predicted 50% mortality at 1 month, irrespective of co-morbidity.

Conclusion. The type of ADI is an important determinant of survival, particularly in patients with preserved CD4 counts. The stratification of patients by type of ADI and performance status may be useful in the management of patients with advanced HIV infection in resource-limited environments.

S Afr Med J 2001; **91**: 583-586.

The disease burden caused by HIV infection has been overwhelming health care facilities in many African countries.[1] It has been suggested that African patients with HIV infection have an increased rate of progression from asymptomatic HIV infection to AIDS compared with patients in the developed world, and this difference has been related to limited access to

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medical care.[1] However, a recent longitudinal cohort study from Uganda[2] showed the rate of progression to AIDS in HIV-positive patients to be comparable to figures previously reported from the Western world. Survival of South African AIDS patients, provided with adequate medical care, has been shown to be similar to that of European and American patients with AIDS.[3]

Laboratory markers that reflect the degree of immune compromise in HIV infection, such as CD4+ T-lymphocyte (CD4) count[4] and quantitative HIV viral load,[5] are frequently unavailable in Africa. In this setting, prognostic information may be obtained from clinical staging as proposed by the World Health Organisation (WHO) clinical staging system and the total lymphocyte count.[2,6,7]

AIDS includes a variety of opportunistic diseases that may occur across a spectrum of immune dysfunction.[8] The prognosis for patients with AIDS varies accordingly and is influenced significantly by the type of AIDS-defining illness (ADI).[3,9,10] Prognostic stratification based on ADI and performance status can be performed in the outpatient clinic and does not require sophisticated laboratory facilities. It is therefore widely applicable in resource-poor settings, and potentially useful to guide resource allocation and patient management. This study evaluated outcome of the commonest AIDS-defining events and poor performance status in a cohort of South African HIV-positive patients.

METHODS

All patients with an AIDS diagnosis (as defined by the proposed WHO clinical staging system,[11] which is similar to the Centers for Diseases Control 1987 definition of AIDS[12]) attending the HIV outpatient clinics of the University of Cape Town medical school (at Somerset and Groote Schuur hospitals) were selected from computer-based medical records. From 1984 to 1997, patients with HIV infection were regularly followed up at these clinics at 6-monthly intervals during the asymptomatic phase of their illness, more frequently as opportunistic infections occurred. At each visit, patients were staged according to the WHO clinical staging system, retrospectively until 1992, prospectively thereafter,[3] and CD4 counts were regularly performed. Tertiary care diagnostic facilities such as bronchoscopy, liver and bone marrow biopsies, microbiology and computed tomography (CT) scanning, were available to confirm the presence of AIDS-related illnesses. These clinics mainly served the underprivileged communities, where heterosexually acquired HIV infection had been increasingly prevalent. However, before 1991 the majority of clinic attendees had been white male homosexuals.[3]

Patients with AIDS or CD4 counts below 200/µl routinely received co-trimoxazole prophylaxis since 1996, and standard treatment for tuberculosis (TB), herpes simplex infection (HSV),

oesophageal candidiasis, *Pneumocystis carinii* pneumonia (PCP) and cryptococcal meningitis was available. Antiretroviral therapy was not routinely available for patients with AIDS, and 48 patients who had received such therapy were excluded from analysis.

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. Status of patients discharged from the clinic for terminal care was obtained from the Red Cross Home-Based Care Society.

Survival was analysed from the first presentation at either clinic according to type of ADI, for diseases that occurred in at least 10 patients. If two or more ADIs occurred simultaneously, patients were placed in the group according to the event with the worst outcome. Survival of patients with AIDS was also analysed according to CD4 count (< 50, 51 - 200, > 200/µl), and for patients with performance status 4 (in bed > 50% of normal day time during the last month). CD4 counts performed within 3 months (before or following) onset of AIDS-related illnesses were used for analysis.

Survival was calculated in months from the index visit (first visit at which the condition occurred) to the date of death or last visit (censored), using Epi-info (version 6). Kaplan-Meier survival curves were created using the software package Statistica (version 6), and evaluated for statistical difference by log-rank test. Relative hazards of death and 95% confidence intervals (CIs) were calculated using the univariate Cox proportional hazard model and Fisher's exact test.

RESULTS

From May 1984 to April 1997, 1 735 patients with HIV infection were seen during 11 493 visits. By April 1997, 280 patients had developed AIDS, and 160 of this number had died. Of the 120 patients alive at the end of the study, 45 had been lost to follow-up after a median clinic attendance of 8.7 months (range 1 - 63 months). Median follow-up for patients with AIDS who were still alive at the end of the study period was 10.2 months (range 1 - 65 months), and 9.7 months (0 - 114) for those who had died. The median number of clinic visits for patients with AIDS was 5 (range 1 - 47), the mean age of patients was 33 years (range 17 - 75 years), and both homosexual (N = 109) and heterosexual (N = 171) transmission patterns, male (N = 199) and female (N = 81) gender, and the three major population groups (76 whites, 75 coloureds and 129 blacks) were represented. Intravenous drug abuse and haemophilia did not occur as risk factors for HIV infection in our patients. Both patients who were diagnosed HIV-positive on presentation at either clinic with an ADI (N = 143) and patients who developed AIDS during follow-up from WHO clinical stages 1 - 3 (N = 137) were represented in this cohort. The total number of ADIs diagnosed in our cohort was 430 (average per patient 1.54); the

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eight diseases mentioned in Table I occurred 317 times (261 as initial ADI).

The overall median survival time from the onset of AIDS was 11.5 months. Initial ADIs were stratified into early, intermediate and late events, according to median survival rates (Table I). There was no statistical difference for the survival curves of individual diseases within each stratum (P = 0.90, 0.43, and 0.98 respectively). Kaplan-Meier survival for each of the three strata of opportunistic diseases is depicted in Fig. 1. Performance status score 4 predicted 50% 1-month mortality, irrespective of co-morbidity.

Survival of AIDS patients was related to both CD4 count and ADI. The relative risk of death for patients with early, intermediate and late diseases within defined strata of CD4 counts is shown in Table II. The influence of ADI on mortality was most striking in patients with relatively preserved CD4 counts.

DISCUSSION

This study, undertaken in a resource-limited environment, showed that the type of ADI was a major predictor of outcome, and that the opportunistic disease could be used as a prognostic adjunct to the CD4 count. Stratification of patients according to ADI and performance status is easily performed, and therefore widely applicable in resource-poor settings. The prognostic information provided by these clinical parameters can be used for counselling and management of HIV-infected patients.

Extrapulmonary TB and HSV infection (lasting more than 1 month) as initial AIDS diagnoses were associated with the most favourable outcome and survival was comparable to reported figures from the developed world.[9,10] Extrapulmonary TB was the initial AIDS diagnosis in one-third of our patients, and was
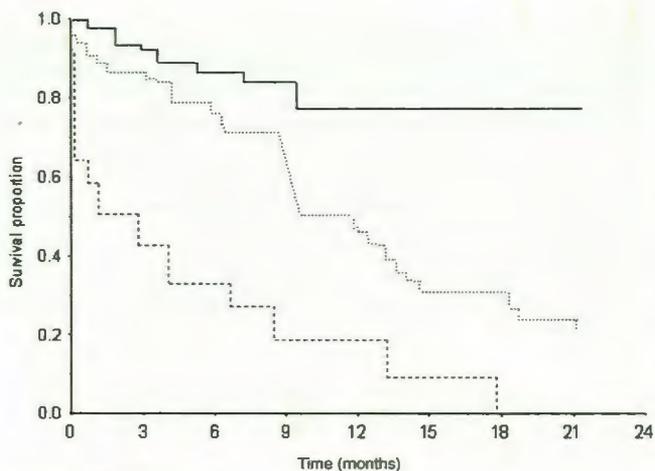
Fig. 1. Survival for the eight commonest AIDS-defining illnesses could be stratified into one of three patterns: early diseases include extrapulmonary TB and HSV, intermediate diseases KS, oesophageal candidiasis, PCP and cryptococcal meningitis, late diseases encephalopathy and wasting. Survival was significantly different for early (solid line), intermediate (dotted line) and late events (intermittent line) (P < 0.00001).

associated with a relatively preserved CD4 count. Our diagnostic facilities allowed for early detection and treatment of extrapulmonary TB, which may explain the more favourable overall prognosis for patients with AIDS in Cape Town compared with Uganda.[2,3]

Survival in our patients following cryptococcal meningitis was similar (7 v. 9 months) to survival of patients with cryptococcosis in a large European study,[10] and predicted outcome for Kaposi's sarcoma (KS) was similar to that in an American cohort (12 v. 12.3 months).[13] The comparability of

Table I. Median CD4 counts and survival (Kaplan-Meier estimates) for the commonest initial AIDS-defining illnesses

AIDS-defining illness	Median CD4 count (range)	Median survival (mo. from diagnosis)	12-month survival (%)	Patients (N)
Early	111	> 24	68	116
Extrapulmonary TB	111 (5 - 990)	> 24	71	97
Herpes simplex virus	114 (8 - 294)	> 24	66	19
Intermediate	48	9	44	105
Kaposi's sarcoma	118 (10 - 581)	12	58	24
Oesophageal candidiasis	76 (1 - 403)	9	52	32
Pneumocystis carinii pneumonia	39 (8 - 155)	7	39	38
Cryptococcal meningitis	32 (9 - 200)	7	23	11
Late	64	2	23	40
Encephalopathy	121 (9 - 393)	3	21	20
Wasting	45 (1 - 755)	1	24	20

Initial AIDS-defining illnesses were stratified into early, intermediate and late events according to median survival rates (> 12, 6 - 12, < 6 months). N reflects the number of patients in each stratum, and median survival is expressed in months from diagnosis.

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Table II. Relative hazards for death associated with class of AIDS-defining illness and defined CD4 count strata. Values for intermediate (Kaposi's sarcoma, oesophageal candidiasis, PCP and cryptococcal meningitis) and late diseases (encephalopathy and wasting) are expressed relative to the risk of early diseases (extrapulmonary TB and herpes simplex) in the same CD4 count stratum. Figures in brackets represent 95% confidence intervals

CD4 count	Class of AIDS-defining illness		
	Early	Intermediate	Late
> 200/µl	1	10.50 (1.60 - 88.90)	21.00 (1.83 - 240.50)
51 - 200/µl	1	3.18 (1.98 - 4.70)	4.33 (1.88 - 30.90)
0 - 50/µl	1	1.39 (0.50 - 3.56)	2.90 (1.60 - 5.00)

African and Western AIDS survival figures supports the notion that access to care is an important determinant of the survival of African AIDS patients.[1]

Reports from sub-Saharan Africa suggest that wasting syndrome is common,[1,2] and post-mortem studies have revealed that TB is highly prevalent in cachectic African AIDS patients.[14] HIV-positive patients who presented to our clinics with a wasting illness were thoroughly investigated for TB by means of sputum smears and culture, histology of lymph node, liver or bone marrow, and blood culture. The resulting high frequency with which TB was diagnosed, and the relatively low prevalence of diarrhoeal illnesses in South African HIV-positive patients,[15] may account for the small number of patients with unexplained HIV-wasting syndrome in this study.

The type of ADI,[9,10] prior HIV or AIDS-related morbidity,[16] total lymphocyte count[5,6] and performance status[17] all provide useful prognostic information in patients with advanced HIV infection. This study has grouped opportunistic illnesses into three categories, as cases were recruited from a single site and hence numbers for individual diseases were small. Although the survival difference for the three groups was marked, and the outcome for each group is consistent with our clinical observations, we cannot exclude the possibility that these differences occurred by chance because of *post hoc* classification. Our stratification would therefore need to be validated prospectively in an African setting.

Prognostic stratification of HIV-infected patients is particularly relevant in resource-poor countries in order to avoid irrational spending of scarce health care resources. Expensive investigations or therapy could then be limited to patients with favourable prognostic criteria. Survival figures of patients with performance status 4 or diseases such as HIV wasting syndrome or encephalopathy, on the other hand, supports the institution of home-based terminal care for these patients.

References

1. Colebunders RL, Latif AS. Natural history and clinical presentation of HIV-1 infection in adults. *AIDS* 1991; 5: suppl 1, S103-S112.
2. Morgan D, Maude GH, Malamba SS, *et al*. HIV-1 disease progression and AIDS-defining disorders in rural Uganda. *Lancet* 1997; 350: 245-250.
3. Maartens G, Wood R, O'Keefe E, Byrne C. Independent epidemics of heterosexual and homosexual HIV infection in South Africa — survival differences. *QJM* 1997; 90: 449-454.
4. Fahey JL, Taylor JMG, Detels R, *et al*. The prognostic value of cellular and serologic markers in infection with human immunodeficiency virus type 1. *N Engl J Med* 1990; 322: 166-172.
5. Saag MS, Holodniy M, Kuritzkes DR, *et al*. HIV viral load markers in clinical practice. *Nat Med* 1996; 2: 625-629.
6. Post FA, Wood R, Maartens G. CD4 and total lymphocyte count as predictors of HIV disease progression. *QJM* 1996; 89: 505-508.
7. Montaner JSG, Le TN, Le N, Craib KJP, Schechter MT. Application of the World Health Organisation system for HIV infection in a cohort of homosexual men in developing a prognostically meaningful staging system. *AIDS* 1992; 6: 719-724.
8. Crowe SM, Carlin JB, Stewart KI, Lucas CR, Hoy JF. Predictive value of CD4 lymphocyte numbers for the development of opportunistic infections and malignancies in HIV-infected persons. *J Acquir Immune Defic Syndr Hum Retrovirol* 1991; 4: 770-776.
9. Luo K, Law M, Kaldor JM, McDonald AM, Cooper DA. The role of initial AIDS-defining illness in survival following AIDS. *AIDS* 1995; 9: 57-63.
10. Mocroft A, Johnson MA, Phillips AN. Factors affecting survival in patients with the acquired imunodeficiency syndrome. *AIDS* 1996; 10: 1057-1065.
11. WHO global programme on AIDS. Proposed World Health Organisation staging system for HIV infection and disease. *AIDS* 1993; 7: 711-718.
12. Centers for Diseases Control. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *Mor Mortal Wkly Rep* 1987; 36: suppl 1, 1S-15S.
13. Chang HH, Morse DL, Noonan C, *et al*. Survival and mortality patterns of an acquired immunodeficiency syndrome (AIDS) cohort in New York state. *Am J Epidemiol* 1993; 138: 341-349.
14. Lucas SB, De Cock KM, Hounnou A, *et al*. Contribution of tuberculosis to slim disease in Africa. *BMJ* 1994; 308: 1531-1533.
15. O'Keefe EA, Wood R. AIDS in Africa. *Scand J Gastroenterol* 1996; 31: suppl 220, 147-152.
16. Mocroft AJ, Lundgren JD, D'Arminio Monforte A, *et al*. Survival of AIDS patients according to type of AIDS-defining event. *Int J Epidemiol* 1997; 26: 400-407.
17. Whittle H, Egboga A, Todd J, *et al*. Clinical and laboratory predictors of survival in Gambian patients with symptomatic HIV-1 or HIV-2 infection. *AIDS* 1992; 6: 685-689.