

Measurable Predictive Factors for Progression to AIDS among HIV-infected Patients in Singapore

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Abstract

Introduction: This study identifies measurable factors at the time of diagnosis that predict the progression to Acquired Immunodeficiency Syndrome (AIDS) among Human Immunodeficiency Virus (HIV)-infected patients in Singapore. **Materials and Methods:** We carried out a retrospective study of 790 HIV-infected patients from 16 May 1985 to 31 December 2001. The end-point was the onset of AIDS-defining illness listed in the 1987 and 1991 revised Centers for Disease Control and Prevention criteria, but excluded CD4 cell counts as a criterion. Using the Kaplan-Meier method, AIDS-free survival curves were plotted for age groups at diagnosis, baseline CD4 counts and periods for utilisation of antiretroviral treatment. A Cox regression model was constructed to determine independent predictors of disease progression. **Results:** Univariate analysis showed that patients of older age at diagnosis had a significantly higher risk of progression compared to younger patients, and patients with higher baseline CD4 cell counts had a lower risk of progression to AIDS. Adjusting for the simultaneous influence of several covariates on the rate of HIV progression to AIDS, multivariate analysis using the Cox model showed a significantly higher risk of progression for older patients at diagnosis, and the progressive lowering of risk with increasing baseline CD4 cell counts. **Conclusions:** This study found older age at diagnosis and baseline CD4 cell counts to be measurable predictors for HIV progression to AIDS at time of diagnosis. Identification of these risk factors enables physicians to provide counselling and advice, and to start appropriate treatment early. This could lower the risk of progression and improve survival.

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Key words: Age, AIDS, CD4 cell counts, HIV infection, Risk factors

Introduction

The first case of human immunodeficiency virus (HIV) infection was detected in Singapore on 16 May 1985. The number of newly diagnosed HIV/acquired immunodeficiency virus syndrome (AIDS) infections has been increasing since 1985, and a total of 1599 cases were detected as of December 2001. In a known cohort of HIV-positive patients, a proportion of patients will progress from HIV to AIDS every year. In 2001 alone, a total of 49 patients previously diagnosed with asymptomatic HIV infection progressed to AIDS.¹

The clinical course of HIV disease is variable; a number of risk factors may influence the natural history of the

infection. Risk factors affecting the progression to AIDS can be constant or variable.² Variable factors, such as CD4 counts, appear at different stages of immunodepression after HIV infection; therefore, they are time-dependent. Constant factors, such as age at seroconversion and mode of infection, are present at the time of infection and remain unchanged.

Several studies have suggested that age at seroconversion influences the onset of AIDS.²⁻¹⁵ The CD4 level has been recognised as a surrogate marker for HIV infection and the most important prognostic indicator for the development of AIDS.¹⁶ A few seroconverter studies have compared HIV progression by different exposure categories,

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and there were differences in findings among these studies.^{2,3,5-7,17,18}

The problem in managing HIV/AIDS patients is that these patients do not usually present at time of infection due to the long asymptomatic phase. Prognostic factors, such as CD4 counts and age, would have changed by the time these patients see their physicians. This study identifies measurable factors at the time of diagnosis so physicians can provide counselling and advice, and decide which patient may benefit from antiretroviral treatment (ART) based on the values of these predictors at time of diagnosis.¹⁹

Materials and Methods

A retrospective study was conducted using data obtained from the National HIV registry. The period of study was 16 May 1985 to 31 December 2001. Basic demographic information, such as age at diagnosis, gender, ethnic group, occupation and mode of transmission, and clinical information including baseline CD4 cell counts, were extracted based on the dates of reported positive Western-Bloc (WB) tests. The extraction process was not patient-identifiable.

The exclusion criteria include patients who were found to have AIDS at first diagnosis, patients who defaulted follow-up and those without baseline CD4 cell counts or those who died from causes other than AIDS. This study focused on the progression among those infected through the sexual mode since it constituted 96.6% of transmission among Singaporeans, and excluded those who were infected by other means. Patients who contacted the disease via the sexual mode were classified as heterosexual, homosexual and bisexual as defined by their stable sexual behaviour.

The length of time from the first positive confirmatory HIV test to the onset of the first AIDS-defining disease was used as the time of progression from HIV to AIDS. The utilisation of antiretroviral therapies was modelled in 3 periods: single therapy or no therapy (before July 1995); single, dual therapies or no therapy (July 1995 to June 1996); single, dual, multiple therapies or no therapy (July 1996 onwards). This approach was based on the evolution of antiretroviral therapies used in the local setting.

Statistical Analysis

The date of HIV infection was estimated using the date of positive WB test. The end-point was the onset of AIDS-defining illness listed in the 1987 and 1991 revised Centers for Disease Control and Prevention (CDC) criteria but excluded CD4 cell counts as a criterion. Patients were noted to have progressed to AIDS based on the occurrence of one or more of the specific indicator opportunistic diseases.²⁰ An event is said to have occurred if the HIV patient progressed to AIDS, and a patient is considered as

a censored case if he or she had not progressed to AIDS at the cut-off date of 31 December 2001.

Using the Kaplan-Meier method, AIDS-free survival curves were plotted for age groups at diagnosis, CD4 count group and period of utilisation of ART. The cumulative numbers of events (i.e., progression to AIDS) by group are shown at the bottom of the survival curves. We classified the baseline CD4 counts using the CDC 1993 classification system for HIV disease.²¹

A Cox regression model was constructed to determine independent predictors of disease progression. The covariates were gender, ethnic group, age at diagnosis, occupation, mode of sexual transmission, period for utilisation of ART and baseline CD4 counts at diagnosis. The proportionality assumption of the multivariate Cox model was tested by examining the parallelism between the log minus log function plots for different values of each covariate, and by including each covariate as a time-dependent term (defined as the interaction between the natural logarithm of the time and the covariate). No significant time-dependent covariates were found.

For disease progression, we analysed the data of patients who did not have a diagnosis of AIDS and used the time of progression from HIV to AIDS as the dependent variable. Statistical significance was taken as $P < 0.05$. Follow-up after 31 December 2001 was not considered for those who had not progressed to AIDS by then.

Results

A total of 790 patients were included in the study, and follow-up was completed through January 2002 with 3675 person-years of observation, giving a median follow-up of 4 years.

The baseline characteristics of the patients are summarised in Table 1. Fifty-two per cent had baseline CD4 cell counts $>200 \text{ mm}^3$ and 66% were diagnosed as being positive for HIV infection in the period when multiple therapies were available.

The median age at diagnosis was 34 years (range, 17 to 8). A total of 236 (29.9%) patients developed AIDS during follow-up.

The AIDS-free survival curves for the age group ≥ 40 years consistently went below that for the age group ≤ 39 years, suggesting a significant increase in the risk of progression to AIDS for those aged ≥ 40 years (Fig. 1). The curves representing baseline CD4 cell counts show distinct separation from the onset and the pattern continues throughout the period of study (Fig. 2). Kaplan-Meier estimate of progression, stratified by period for utilisation of ART, showed faster progression to AIDS for the second period; the curve for the second period was consistently below that for the first period. The progression to AIDS

Table 1. Characteristics of Patients (n = 790)

Characteristic	No. of patients (%)	AIDS (% of those with the characteristics)	<i>P</i> value*
Gender			
Male	675 (85.4)	213 (31.6)	0.08
Female	115 (14.6)	23 (20.0)	
Ethnic group			
Chinese	675 (85.4)	197 (29.2)	0.88
Malay	35 (4.4)	13 (37.1)	
Indian	47 (6.0)	17 (36.2)	
Others	33 (4.2)	9 (27.3)	
Age at diagnosis (y)			
<30	223 (28.2)	70 (31.4)	0.01
30-39	318 (40.3)	99 (31.1)	
40-49	150 (19.0)	40 (26.7)	
>50	99 (12.5)	27 (27.3)	
Occupation			
Professional/Executive	166 (21.0)	47 (28.3)	0.21
Administrative/Service-oriented	212 (26.8)	65 (30.7)	
Labour-intensive	233 (29.5)	63 (27.0)	
Unemployed	179 (22.7)	61 (34.1)	
Mode of sexual transmission			
Heterosexual	604 (76.5)	173 (28.6)	0.61
Homosexual	104 (13.2)	36 (34.6)	
Bisexual	82 (10.4)	27 (32.9)	
Period for utilisation of ART			
16 May 1985-30 June 1995	212 (26.8)	120 (56.6)	0.23
1 July 1995-31 June 1996	57 (7.2)	28 (49.1)	
1 July 1996-31 December 2001	521 (66.0)	88 (16.9)	
Baseline CD4 counts (mm³)			
0-199	379 (48.0)	167 (44.1)	<0.001
200-500	306 (38.7)	54 (17.6)	
>500	105 (13.3)	15 (14.3)	

* Based on comparison of Kaplan-Meier curves for progression to AIDS using Breslow test.

AIDS: acquired immunodeficiency virus syndrome; ART: antiretroviral therapies

was slower for the third period (Fig. 3).

Univariate analysis showed no significant differences in gender, ethnic group, occupation, mode of sexual transmission and period for utilisation (Table 2). Patients of older age at diagnosis were at higher risk of progression to AIDS. For baseline CD4 counts, univariate analysis showed a significantly lower risk of progression to AIDS at higher cell counts for the whole range. The third period (1 July 1996 to 31 December 2001) showed significant slowing down of progression to AIDS compared to the first period (16 May 1985 to 30 June 1995).

Adjusting for the simultaneous influence of several covariates on the rate of AIDS progression, multivariate analysis showed significantly higher risk of progression for patients of older age at diagnosis, and progressive lowering of the risk of progression with increasing baseline CD4 cell counts. For utilisation of ART, multivariate analysis showed that the second period was associated with a 47% increase

in risk of progression to AIDS [hazard ratio (HR), 1.47; 95% confidence interval (CI), 0.95 to 2.29] compared to the first period. Progression to AIDS slowed down in the third period when patients could receive multiple therapies, but the difference was non-significant (Table 2). In our study, combining the second and third periods (1 July 1995 to 31 December 2001) showed non-significant slowing of progression to AIDS when compared with the analysis using 3 periods (HR, 0.95; *P* = 0.72; 95% CI, 0.7 to 1.29). The clinical indicator of low baseline CD4 cell counts was found to be the single variable most predictive of an early progression to AIDS.

Discussion

Understanding the natural progression of HIV infection is important in clinical management, counselling prevention and treatment strategies.⁵

The influence of age at diagnosis was clear in this study population, where those of older age progressed to AIDS

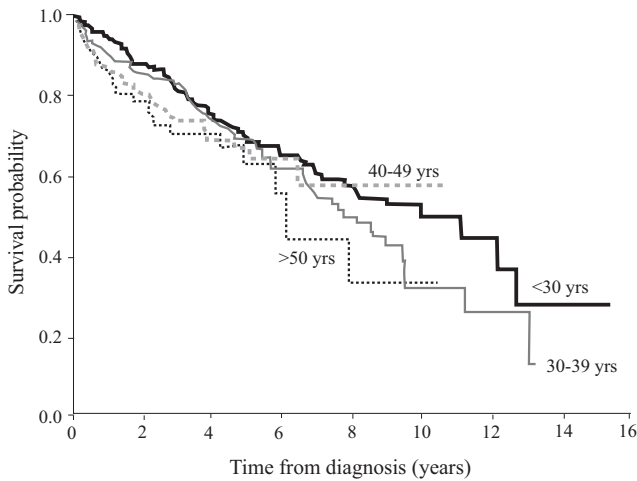


Fig. 1. Kaplan-Meier estimates of survival stratified by age group at diagnosis.

Cumulative number of events

<30 years	25	45	57	64	67	68	70	70
30-39 years	43	64	81	90	97	98	99	99
40-49 years	27	36	38	39	39	39	39	39
>50 years	17	21	24	27	27	27	27	27

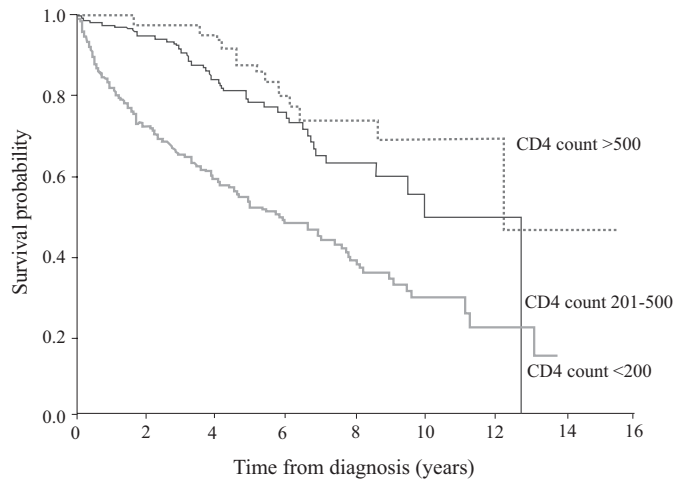


Fig. 2. Kaplan-Meier estimates of survival stratified by baseline CD4 counts.

Cumulative number of events

CD4 <200	96	128	145	157	163	165	166	166
CD4 201-500	14	34	43	50	53	53	54	54
CD4 >500	2	4	11	13	14	14	15	15

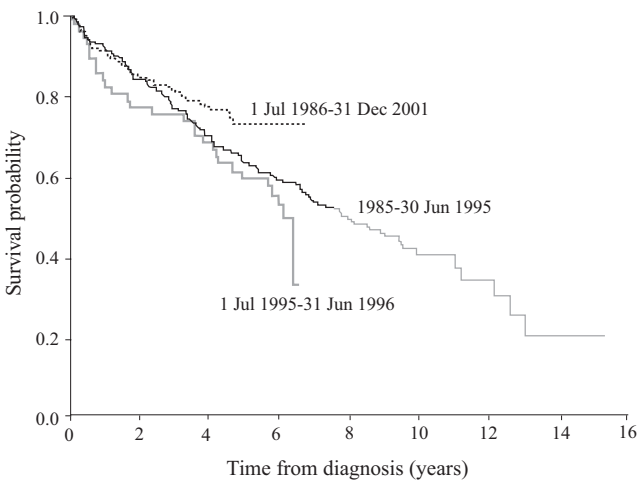


Fig. 3. Kaplan-Meier estimates of survival stratified by period for utilisation of antiretroviral therapies.

Cumulative number of events

16 May 1985-30 June 1995	33	64	87	104	115	117	120	120
1 July 1995-31 June 1996	13	18	26	28	28	28	28	28
1 July 1996-31 Dec 2001	66	83	87	87	87	87	87	87

at a faster rate. This finding concurs with several studies that supported the role of advancing age in predicting a faster progression.²⁻¹⁵ Low CD4 counts were associated with age at diagnosis, suggesting a rapid decline of this lymphocyte subset in older subjects or late presentations.²² This decrease could be due to a deterioration in thymic function, as suggested by studies which show that the

capacity to produce new CD4 cells after chemotherapy is inversely related to the patient's age.^{23,24} Thus, older subjects may have a reduced capacity to generate new CD4 cells in response to the viral killing.^{25,26}

Several studies support our findings that low CD4 counts are most predictive of an early progression to AIDS.^{10,14,27,28} Therefore, it may be more meaningful to use the level of CD4 as a clinical indicator for disease progression. The 1993 expanded AIDS surveillance case definition includes all HIV-infected persons who have <200 CD4 cell counts, which helps to reflect more accurately the number of persons with severe HIV-related morbidity and immunosuppression and to simplify the reporting process. More detailed study of the determinants of CD4 decline would be valuable in uncovering factors associated with disease progression not detected in this study.^{29,30}

The use of baseline CD4 counts as a surrogate for CD4 counts at time of infection in this study has created a potential problem in that the exact age at infection could not be extracted from our records, especially the asymptomatic cases. It is possible that these patients could have been infected earlier and, therefore, they should belong to younger age groups in the analyses. This could potentially diminish the differences in the findings we have seen among the age groups.

In this study, we modelled the periods for receiving antiretroviral therapies according to the availability of commercial ART products and our pharmaceutical sales records. The 3 periods were similar to those used by Rogers et al³¹ for their study on survival after the diagnosis of AIDS

Table 2. Progression to AIDS in Patients with HIV but without AIDS (n = 790)

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Gender			<i>0.19</i>			<i>0.26</i>
Male	1.00	Referent		1.00	Referent	
Female	0.75	0.49-1.16		0.73	0.43-1.25	
Ethnic group			<i>0.96</i>			<i>0.68</i>
Chinese	1.00	Referent		1.00	Referent	
Malay	1.15	0.66-2.02	0.63	1.34	0.74-2.42	0.33
Indian	1.02	0.62-1.68	0.94	1.02	0.61-1.70	0.93
Others	1.08	0.56-2.11	0.82	1.42	0.64-3.14	0.39
Age at diagnosis	1.02	1.01-1.03	<i>0.003</i>	1.02	1.01-1.03	<i>0.006</i>
Occupation			<i>0.59</i>			<i>0.74</i>
Professional/Executive	1.00	Referent		1.00	Referent	
Administrative/Service-oriented	1.20	0.82-1.74	0.35	1.18	0.80-1.73	0.41
Labour-intensive	1.19	0.81-1.74	0.37	1.17	0.79-1.73	0.43
Unemployed	1.31	0.89-1.91	0.17	1.25	0.84-1.87	0.28
Mode of sexual transmission			<i>0.86</i>			<i>0.66</i>
Heterosexual	1.00	Referent		1.00	Referent	
Homosexual	0.98	0.68-1.41	0.93	1.07	0.72-1.59	0.75
Bisexual	0.89	0.59-1.35	0.59	0.85	0.55-1.29	0.44
Period for utilisation of ART			<i>0.05</i>			<i>0.04</i>
16 May 1985-30 June 1995	1.00	Referent		1.00	Referent	
1 July 1995-31 June 1996	1.30	0.85-1.99	0.23	1.47	0.95-2.29	0.08
1 July 1996-31 December 2001	0.78	0.57-1.06	0.12	0.82	0.59-1.14	0.24
Baseline CD4 counts (per mm ³)			<i><0.001</i>			<i>0.66</i>
0-199	1.00	Referent		1.00	Referent	
200-500	0.36	0.27-0.49	<i><0.001</i>	0.37	0.27-0.51	<i><0.001</i>
>500	0.23	0.14-0.40	<i><0.001</i>	0.23	0.14-0.39	<i><0.001</i>

Overall *P* values of the covariates are in italics. AIDS: acquired immunodeficiency virus syndrome; ART: antiretroviral therapies; CI: confidence interval; HIV: human immunodeficiency virus; HR: hazard ratio

in an era of multiple therapies. They found that survival rates worsened in the second period and improved in the third period for heterosexual females and homosexual males. In this study, the risk of progression decreased by 18% (though a statistically significant level was not reached) in the period when multiple drugs were used. Further analysis by combining periods where dual or multiple drugs were used did not show significant slowing of progression to AIDS compared to the results obtained from analysing the 3 periods. Several other studies have shown reductions in disease progression and survival with the introduction of antiretroviral combination therapies.³²⁻³⁶ Inaccurate diagnosis dates, wide variations in the sample sizes of the 3 periods, failure to define AIDS accurately using CD4 cell count depletion, and low consumption and compliance could have accounted for the lack of significant difference in our study. In addition, because our analysis was based on non-randomised observational data, it was possible that unmeasured selection factors related to the physicians' and patients' decisions on the use of combination therapies could have affected our results.

Disease progression was not related to gender, ethnic

group, occupation and mode of sexual transmission. Other studies have shown similar results.^{3,10,14,37} Our data support the hypothesis that when equal access to healthcare is provided, the outcomes would be similar for different genders, ethnic groups, occupations and modes of sexual transmission.

Loss to follow-up was a potential source of bias in this study. The exact time of infection was unknown and was estimated using the dates of positive WB tests; this could be the reason the study failed to detect differences in progression among the different groups of sexual exposure. However, a study on haemophiliac patients, for whom the date of infection was either known or estimated accurately, has clearly demonstrated that time since infection has no independent prognostic significance once CD4 cell counts are taken into account.³⁸

In conclusion, this study found older age at diagnosis and baseline CD4 cell counts to be measurable predictors for HIV progression to AIDS. Identification of these risk factors will enable physicians to provide counselling and advice, and to start appropriate treatment early. This could lower the risk of progression and improve survival.

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