Original Article

Presentation and Outcome Amongst Older Singaporeans Living with Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS): Does Age Alone Drive Excess Mortality?

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Abstract

Introduction: There is little detailed information on human immunodeficiency virus (HIV) amongst older adults in Singapore. Materials and Methods: A retrospective study of 121 consecutive referrals of patients presenting for HIV care was conducted. Demographic, clinical and laboratory variables were collected. A prognostic model derived from the North American Veterans' Affairs Cohort Study (VACS) was used to estimate prognosis. Results: The median age at presentation was 43 (range, 18 to 76). Thirty-eight patients (31%) were aged 50 or older and 106 patients (88%) were male. Older patients were more likely to be of Chinese ethnicity ($P = 0.035$), married ($P = 0.0001$), unemployed or retired ($P = 0.0001$), and to have acquired their infection heterosexually ($P = 0.0002$). The majority of patients in both groups were symptomatic at presentation. Eighty-one (67%) had CD4 counts less than 200 at baseline with no observable differences in HIV ribonucleic acid (RNA) or clinical stage based on age. Non-Acquired Immunodeficiency Syndrome (AIDS) morbidity was observed more frequently amongst older patients. The estimated prognosis of patients differed significantly based on age. Using the VACS Index and comparing younger patients with those aged 50 and above, mean 5 year mortality estimates were 25% and 50% respectively ($P < 0.001$). A trend towards earlier antiretroviral therapy was noted amongst older patients ($P = 0.067$) driven mainly by fewer financial difficulties reported as barriers to treatment. Conclusion: Older patients form a high proportion of newly diagnosed HIV/AIDS cases and present with more non-AIDS morbidity. This confers a poor prognosis despite comparable findings with younger patients in terms of clinical stage, AIDS-defining illness, CD4 count and HIV viral load.

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Key words: AIDS, Ageing, HIV, Prognosis

Introduction

Singapore is a country of high income with a low level human immunodeficiency virus (HIV) epidemic, the yearly incidence of disease currently standing at 121.7 new infections per million population per year.[1-3] Certain features of Singapore's HIV epidemic are notable. Firstly, despite active screening programmes amongst high-risk populations and adult hospital in-patients, more than half of newly notified patients have advanced HIV infection at diagnosis (defined as an Acquired Immunodeficiency Syndrome (AIDS)-defining illness or CD4 count <200) and an even higher proportion are diagnosed in the course of medical assessment.[2,4-6] Secondly, the ratio of male to female infections has been 9:1 or higher since the beginning of the epidemic, which now stands in stark contrast to the region of southeast Asia where 35% of infections are amongst women.[7] Thirdly, the proportion of older patients amongst people living with HIV and AIDS (PLWHA) in Singapore is very high. Twenty-eight percent of patients diagnosed between 2005 and 2011 were 50 and above and 36% of this group were 60 or older.[3]

In many countries, non-AIDS illnesses now cause the majority of deaths in HIV infected patients under long-term follow-up.[8,9] There is an increasing realisation that these morbidities are a manifestation of HIV infection and/or its treatment, not simply the consequence of survival to an older age on therapy.[8] The presence and persistence of immune dysfunction and chronic inflammation before and after initiation of combination antiretroviral therapy (cART) have been linked to end-organ dysfunction and the accelerated expression of non-AIDS morbidity. These

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phenomena may be exaggerated with age and are thought to explain why cART does not fully restore health or lifespan in older PLWHA.[8-10]

There is little research into HIV in older patients originating from high income economies outside the United States (US) and Europe. Given the high proportion of older HIV infected patients in our clinics, we sought to compare those aged 50 and over with younger patients presenting for care at our hospital. Our aims were to: (i) update local observations of the clinical and demographic features of HIV-infected patients; and (ii) to explore the presence and potential prognostic impact of end-organ dysfunction and non-AIDS morbidity in each group.

Materials and Methods

The National University Hospital is a 1032-bed academic medical centre situated in the west of Singapore which deals with 135,000 emergency department presentations and 56,000 adult admissions each year. A HIV multidisciplinary service was formally established in 2008 staffed by infectious disease specialists, a nurse clinician, a clinical pharmacist and 2 medical social workers. A registry of new patients was prospectively maintained containing basic demographic details collected in the process of new patient assessment.

A retrospective cohort study was conducted to describe the demographic, clinical and laboratory features of HIV-infected patients based on age. Patients were Singapore citizens and permanent residents entered on the new patient registry. We included patients with a known HIV diagnosis if they had previously been lost to clinical follow-up and were not taking antiretroviral therapy at initial assessment. Patients were excluded if determined to be under active follow-up at another treatment centre. We collected basic demographic and laboratory data and documented the presence or absence of the following at or within 3 months of presentation: (i) AIDS-defining illness; (ii) important co-infections (syphilis, hepatitis B, hepatitis C) and non-AIDS defining episodes of infection indicative of immunodeficiency (i.e. single episodes of bacterial pneumonia or non-typhoidal Salmonella bacteremia); (iii) non-AIDS morbidity linked to chronic inflammation and/or immune dysfunction (categorised as vascular disease (coronary artery disease, cardiomyopathy, thrombosis and stroke), cirrhotic liver disease; infection and non-infection related malignancy, peripheral neuropathy, osteoporosis, avascular necrosis, chronic renal impairment, haematologic abnormality (anaemia/thrombocytopenia); and (iv) mortality and details of cART initiation.

We calculated a prognostic index for each patient using a scoring system developed and validated in the North American Veterans Affairs Cohort Study, the VACS Index.[10] Briefly, the index takes demographic factors, indices of viral replication, CD4+ cell depletion, chronic inflammation (haemoglobin and platelet count), renal impairment and liver fibrosis (inferred using the FIB-4 index)[11] to calculate an estimate of mortality risk over 5 years assuming initiation of cART.[10] In a validation cohort, scores performed equally well as estimates of short-term outcome and discriminated accurately between patients in similar strata of age, CD4 and HIV viral load. Substantial differences between our cohort and the sample of patients taken to derive the VACS Index were accepted as inevitable and necessary in the absence of similar work in an Asian setting. This being an exploratory retrospective study, no additional tests were performed to confirm the presence or absence of liver fibrosis, to directly estimate glomerular filtration rate or to identify age and sex-matched controls.

Data were tabulated using Microsoft Excel™ and additional statistical calculations performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Fisher's exact test, the Mann-Whitney U Test or Student's t-test were used as appropriate. A P value of ≤ 0.05 was used to determine statistical significance. Ethical approval to conduct this study was granted by the National Healthcare Group Domain Specific Review Board.

Results

One hundred and sixty eligible patients were identified of whom 39 were excluded (14 foreigners, 25 under treatment and follow-up at other centres). Of the 121 patients studied, 113 patients were newly diagnosed with HIV, and 8 patients were previously diagnosed with HIV but were not in care.

Demographic and socioeconomic variables are shown in Table 1. Thirty-eight patients were aged 50 or above [median (IQ range); 57 (range, 53 to 66)] and 83 were younger than 50 [median (IQ range); 37 (range, 30 to 44)]. In keeping with national statistics, the male:female patient ratio was high at 9:1 with no differences in the ratio observed based on age. Sixty-six percent of older patients compared with 24% of younger patients were married ($P = 0.0001$) and 90% acquired their infection heterosexually compared with 56% of younger patients ($P = 0.0002$). Only 11% of younger patients were unemployed, with almost half working in administration and service industries.

Details of clinical presentation, disease stage and key laboratory parameters are shown in Table 2. Eighty-seven referrals (72%) were for patients with advanced HIV infection defined as a CD4 count below 200 or an AIDS-defining illness and only 8 were truly asymptomatic even though 25 were diagnosed through screening activities.[12] Half of our patients were classed to be in the World Health

Table 1. Demographics and Socioeconomic Status

	Number of patients and percentage (<50 years old)	Number of patients and percentage (≥50 years old)	*P* value
Total number of patients	83 (68.6%)	38 (31.4%)	NA
Age at presentation (years)			
Median	37	57	NA
Interquartile range	30 to 44	53 to 66	
Gender			
Male	72 (87%)	34 (89%)	0.77
Female	11 (13%)	4 (11%)	
Ethnicity			
Chinese	53 (64%)	32 (84%)	0.035
Malay	25 (30%)	3 (8%)	0.01
Indian	3 (4%)	2 (5%)	0.64
Others	2 (2%)	1 (3%)	1.0
Marital status			
Married	20 (24%)	25 (66%)	0.0001*
Single	51 (62%)	7 (18%)	-
Divorced	9 (11%)	5 (13%)	-
Widowed	1 (1%)	1 (3%)	-
Unavailable data	2	0	-
Employment			
Employed	69 (82%)	18 (47%)	0.0001
Unemployed	9 (11%)	20 (53%)	0.0001
Students	3 (4%)	0	0.55
No data	2 (3%)	0	-
Job			
Professional	11 (13%)	3 (8%)	-
Administrative/ service	38 (46%)	4 (10%)	-
Blue collar	20 (24%)	11 (29%)	-
Student	3 (4%)	0	-
Unemployed/ retired	9 (11%)	20 (53%)	0.0001*
Unavailable data	2	0	-
Mode of transmission			
Heterosexual	46 (56%)	34 (90%)	0.0002
Homosexual	30 (36%)	1 (2.5%)	0.0001
Bisexual	2 (2%)	2 (5%)	NS
Intravenous drug abuse	3 (4%)	1 (2.5%)	NS
No data	2	0	NS

NA: not applicable; NS: non-significant

*compared with all patients in other categories

Table 2. Clinical Presentation and Disease Stage

			P value
Presentation			
Health screening	20 (24%)	5 (13%)	0.2278
Symptomatic	63 (76%)	33 (87%)	
CD4 absolute count (cells/mm^3)			
Median (IQ range)	111 (34 to 240)	88 (22 to 187)	0.255
<50	27 (33%)	14 (37%)	
50 to 99	11 (13%)	6 (16%)	
100 to 199	14 (17%)	9 (24%)	
200 to 349	14 (17%)	2 (5%)	
350 to 499	11 (13%)	5 (13%)	
≥500	6 (7%)	2 (5%)	
<200	52 (63)	29 (76)	0.15
WHO staging at presentation			
1	20 (24%)	7 (18%)	
2	4 (5%)	0	
3	9 (11%)	9 (24%)	
4	41 (49%)	20 (53%)	
Acute seroconversion	9 (11%)	2 (5%)	
Disease stage 1+2*	24 (32%)	7 (19)	0.181
Disease stage 3+4*	50 (68%)	29 (81)	
CDC staging			
A1	6 (7%)	2 (5%)	
A2	16 (19%)	4 (11%)	
A3	8 (10%)	4 (11%)	
B1	0	0	
B2	4 (5%)	2 (5%)	
B3	4 (5%)	6 (16%)	
C1	0	0	
C2	3 (4%)	1 (3%)	
C3	42 (50%)	19 (50%)	
A+B	38 (46%)	18 (47%)	1.0
C	45 (54%)	20 (53%)	
AIDS defining conditions at presentation†			
NIL	38 (46%)	18 (47%)	
PCP	21 (25%)	13 (34%)	
AIDS wasting syndrome	1 (1%)	1 (3%)	
AIDS dementia	1 (1%)	-	
Cryptococcus meningitis	1 (1%)	-	
Cerebral toxoplasmosis	2 (2%)	1 (3%)	
Oesophageal candidiasis	6 (7%)	6 (16%)	
Pulmonary tuberculosis	9 (11%)	1 (3%)	
Extrapulmonary tuberculosis	5 (6%)	2 (5%)	
CMV disease	11 (13%)	6 (16%)	
Mycobacterium avium	3 (4 %)	1 (3%)	
Primary CNS lymphoma	1 (1%)	-	
Non Hodgkin lymphoma	-	1 (3%)	

Table 2. Clinical Presentation and Disease Stage (Con't)

AIDS defining conditions at presentation†			***P* value**
Burkitt's lymphoma	2 (2%)	-	
Recurrent bacterial pneumonia	-	1 (3%)	
Non-AIDS morbidities			
Haematological	7 (8%)	9 (24%)	0.039
Vascular	3 (4%)	6 (16%)	0.026
Renal	0	3 (8%)	0.029
Liver cirrhosis	1 (1%)	0	1.0
Peripheral neuropathy	0	2 (5%)	0.096
Malignancy	1 (1%)	2 (5%)	0.23
NIL	70 (84%)	19 (50%)	0.0001

AIDS: Acquired Immunodeficiency Syndrome; CDC: Centre for Disease Control; CMV: Cytomegalovirus; CNS: central nervous system; IQ: inter quartile; PCP: pneumocystis (carinii) jiroveci pneumonia; WHO: World Health Organization

*amongst patients presenting with chronic HIV infection

†Percentage totals exceed 100% due to patients presenting with more than one AIDS defining condition

Organization (WHO) clinical stage 4 or surveillance category C3 (AIDS Surveillance Case Definition for Adults and Adults: 1993). Sixty-two patients had an AIDS-defining illness at presentation.[13,14] There were no statistically significant differences between groups in relation to clinical stage, CD4 count or HIV viral load.

The frequency of non-AIDS morbidity and the remaining data required to derive a score using the VACS Index are shown in Table 3. There was no difference in HIV RNA between groups. Half of patients aged 50 or over had at least one non-AIDS morbidity with haematologic, vascular and renal disease most frequent. Cirrhotic liver disease and malignancy were infrequent in both groups. Sufficient data were available to derive the VACS Index in 37 older patients and 79 younger patients. The respective mean (±SD) estimates of 5-year mortality risk in each group were 25% (±17.4) and 50% (±21, P <0.0001).

All but 6 patients had an indication to start cART. Seventy-seven patients under 50 (93%) presented with a CD4 count <500 cells/mm^3. A universal recommendation for treatment was made for patients aged 50 and over in the most recent update to treatment guidelines published by the US Department of Health and Human Services (2012 March DHHS guidelines). Eight patients under 50 (10% of the group) and 2 older patients (5% of the group) died within 3 months of diagnosis. We had complete records of treatment at 3 months for 64 of the 70 younger surviving patients and 32 of 36 older patients. Twenty-four (38%) treatment eligible survivors amongst those under 50 had

Table 3. Clinical and Laboratory Data Used to Calculate VACS Index

HIV RNA (log copies/mL)			
<3	1 (1%)	1 (2%)	0.55
3 to 5	28 (34%)	12 (32%)	1.0
>5	49 (59%)	25 (66%)	0.55
Unavailable data	5 (6%)		
Haemoglobin (g/dL)			
≥14	24 (29%)	8 (21%)	-
12 to 13.9	25 (30%)	7 (19%)	-
10 to 11.9	28 (34%)	15 (39%)	-
<10	6 (7%)	8 (21%)	0.035*
Mean (SD)	12.4 (2.29)	11.6 (2.4)	0.062§
eGFR (mL/min)			
≥60	82 (99%)	30 (79%)	-
45 to 59.9	0	3 (8%)	-
30 to 44.9	0	0	-
<30	1 (1%)	5 (13%)	0.0004†
Abnormal (<60)	1 (1%)	8 (21%)	0.0004
Hepatitis C			
No	81 (98%)	38 (100%)	
Yes	2 (2%)	0	1.0
Fib-4 index			
<1.45	59 (71%)	9 (24%)	
1.45-3.25	18 (22%)	19 (50%)	
>3.25	6 (7%)	9 (24%)	
Not documented	0	1 (3%)	
Median (IQ range)	0.97 (0.67, 0.97)	1.81 (1.3, 3.3)	<0.001‡
VACS index 5 year mortality risk (%)			
Patients with complete data	79	37	
Mean estimated 5 year mortality (SD)	25.3 (17.4)	50 (21.05)	<0.0001§

eGFR: estimated glomerular filtration rate; Fib-4: fibrosis stage index; HIV: human immunodeficiency virus; IQ: inter quartile; RNA: ribonucleic acid; SD: standard deviation; VACS: Veterans Aging Cohort Study (Index)[10] a weighted prognostic index combining age, sex, race, CD4 count, HIV RNA, haemoglobin, aspartate aminotrensferase (AST), alanine aminotransferase (ALT), platelet count and the FIB-4 index[11]

*In comparison to all patients in group with haemoglobin >10

†In comparison to all patients in group with eGFR >30mL/min

‡Mann-Whitney U test

§Student t-test

not initiated cART compared with 6 (18%) older patients ($P = 0.067$). Seven younger patients (29%) in this group declined treatment on the basis of cost. No treatment eligible patient aged 50 or older declined treatment on these grounds.

Discussion

This study contributes to the understanding of the epidemiology and clinical presentation of HIV in Singapore. In the southeast Asian context, our observations also support recent insights into the immunopathogenesis of AIDS and non-AIDS morbidity amongst HIV-infected patients.

Lee et al[15] studied 43 cases of HIV infection amongst older patients (aged 50 over) presenting to the Singapore Communicable Disease Centre between 1985 and 1996. The proportion of new patients diagnosed in this age group rose from 4.8% to 16.7% of incident cases over the period studied. Ninety-three percent were heterosexual and 79% were married. Chow et al[16] demonstrated that HIV progresses more quickly to AIDS amongst older Singaporean patients and age has separately been shown to be a major risk for advanced HIV infection at diagnosis (defined as a CD4 count <200 or AIDS-defining illness within 1 year of presentation).[12,17]

One of the most striking features of available data remains the high proportion of infections amongst older men, with a male to female ration of 9:1 observed here. In contrast, 33% of PLWHA in southeast Asia and 50% worldwide are women.[7] National figures for 2011 report a ratio of almost 14:1.[3] The situation resembles the early stages of epidemics in countries before HIV "escaped" from high-risk male populations (i.e. men who have sex with men (MSM), male partners of female sex workers and injecting drug users) to their low-risk female partners.[7] This ratio may be exaggerated and maintained by technical and social factors. Official figures report all infections amongst Singapore citizens and permanent residents and so exclude cases diagnosed amongst female foreign workers and the non-resident (female) partners of Singaporean men. Whereas 38% of younger patients in our study identified themselves as homosexual or bisexual, homosexual sex may be under-reported amongst older patients, both for fear of stigma and because homosexual sex remains a crime under section 377A of the Singapore Penal Code. Singapore does not have a significant number of intravenous drug users (IVDU) compared with other countries in the region and only 3% of our patients were infected by this route.[7] The number of infected female partners of male IVDU in Singapore is therefore likely to be low.

None of the above diminish the importance of heterosexual contact as a major HIV infection risk for older Singaporean men. Consistent with the observations of others,[15] our records suggest that 90% of older patients report this as their only risk factor. It has already been suggested that public and sexual health interventions should target this group, particularly those travelling to nearby countries where HIV infection is increasing in prevalence amongst female sex workers.[15,18-20] In common with other countries in Asia, Singapore has a rapidly ageing population with the proportion of adults aged 65 and over predicted to rise to 20% by 2030.[21] Older patients are therefore a growing population at risk, worthy of prevention efforts and closer attention to symptoms of immunodeficiency presenting during routine health checks.

The growth of research into HIV and ageing is now driven by 3 decades of studies in demography, therapy and biology.[8] Older patients are increasingly represented amongst PLWHA in high and low income economies, both because of an increase in HIV incidence in this group and prolonged survival of patients on cART.[22,23] A unifying theory, reviewed in detail elsewhere, has been proposed suggesting that AIDS and end-organ damage are accelerated in older patients. Cofactors that have been suggested are chronic inflammation, age-related T-cell depletion and senescence, persistent HIV-related immune dysfunction despite virologic suppression, reactivation of latent viral infections (particularly cytomegalovirus), and the effects of HIV treatment and drug toxicity.[8] Consistent with this model of disease progression, older patients in our study suffered more non-AIDS morbidity and presented more frequently with evidence of chronic inflammation and end-organ damage using the indices suggested by Justice et al.[10] This was despite similarity with younger patients in terms of CD4 count, HIV RNA and AIDS-defining illness at presentation. Our finding of higher 5-year mortality estimates using this score is unlikely, therefore, to be driven by age alone and is consistent with the contention that chronic inflammation accelerates non-AIDS morbidity and end-organ disease. The SMART study made it clear that patients exposed to lower CD4 cell counts and higher mean HIV-1 plasma RNA levels demonstrate a strong association between these variables and a wide spectrum of morbidities.[24] Early diagnosis and initiation of cART therefore remain a priority.

This study has several important limitations, not least its retrospective, observational design. Adequate study of the morbidity and prognosis would require a prospective longitudinal study with age and sex-matched controls. We have acknowledged the difficulties inherent to the use of a prognostic index derived from a North American patient cohort. For several reasons, our results cannot be generalised to the Singapore HIV epidemic as a whole. As a new HIV medicine service, very few of our referrals were from screening centres and sexual health clinics. These referrals presumably continue to be made to HIV treatment providers

at other hospitals. Patients diagnosed after undergoing risk-based screening in ambulatory settings are less likely to have advanced infection at diagnosis and we feel that this explains the discrepancy in the proportion of patients diagnosed with AIDS in our cohort compared with national figures. Finally, our observations on risk behaviour are not based on in-depth interviewing for contact tracing purposes.

The rapid ageing of the Singapore population combined with risk behaviours amongst men will continue to shape the local HIV epidemic. Health education for older male patients and effective healthcare planning will be essential both to reduce the burden of infection and manage its consequences.

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