Original Article

Older Age at Initial Presentation to Human Immunodeficiency Virus (HIV) Care and Treatment at the Communicable Disease Centre (CDC) in Singapore, 2006 to 2011

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Abstract

Introduction: The incidence of newly diagnosed older patients diagnosed with human immunodeficiency virus (HIV) has increased worldwide in recent years. In this study, we compared the demographics and clinical presentation of younger and older patients in our HIV sentinel cohort. Materials and Methods: Among all HIV patients presenting to the Communicable Disease Centre (CDC), Singapore from 2006 to 2011, 793 were randomly included in our cohort, representing about 50% of the patients seen during that period. We collected demographic, clinical, laboratory, and outcome data from patient records to compare younger (<50 years old) and older (≥50 years old) HIV patients. Results: Older patients comprised 27.1% of our HIV cohort and presented with lower median CD4 T cell counts (65 cells/mm^3, interquartile range [IQR]: 27 to 214 cells/mm^3) compared to younger patients (250 cells/mm^3, IQR: 74 to 400 cells/mm^3; *P* <0.001). The median time from HIV diagnosis to initiation of antiretroviral therapy (ART) differed significantly for both age groups as well (49 days for patients <50 years old, IQR: 18 to 294 days; versus 35 days for patients ≥50 years old, IQR: 14 to 102 days; *P* = 0.008). More of our younger patients were single (72.2%) or homosexual (44.1%), in contrast to older patients, of whom 48.8% were married and 84.7% were heterosexual. Conclusion: Upon comparison of our younger and older patients, we identified distinct differences in risk transmission and clinical presentation. Increased awareness of older patients at risk of HIV may improve time to diagnosis among this age group.

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Key words: CD4 count, Elderly, HIV/AIDS

Introduction

Since the first case of human immunodeficiency virus (HIV) in Singapore was identified in 1985,[1] the incidence of HIV/acquired immunodeficiency syndrome (AIDS) has steadily increased, reaching a peak rate of 125.2 cases per million population in 2008.[2] From 2006 to 2011, 28.3% of newly diagnosed HIV/AIDS cases in Singapore were aged 50 years and above, an increase from 20.7% during 1985 to 2005.[2] A 1997 study from the Communicable Disease Centre (CDC), Singapore observed an increasing proportion of older HIV patients from 4.8% in 1991 to 16.7% in mid-1996.[3] Altoff et al[4] noted a similar trend in their large North American cohort, in which 17% of newly diagnosed HIV positive cases were aged 50 years and above in 1997 and 27% in 2007.

Recognition of this age group is important because they may not be perceived as high-risk for HIV or other sexually transmitted infections. Patients in this older age group often present with lower CD4 counts and more advanced disease compared to their younger counterparts.[5] In a Swiss HIV cohort, non-AIDS comorbidities such as diabetes mellitus, cardiovascular disease, and osteoporosis were significant risk factors for death in HIV patients aged 50 years and above.[6] One study in Spain noted that older patients are diagnosed with HIV much later during the course of infection,[7] which has implications for prognosis even after receipt of antiretroviral therapy (ART).

In this study, we aimed to compare the presentation and clinical characteristics of older (≥50 years old) and younger (<50 years old) patients presenting to care at the CDC from 2006 to 2011.

Materials and Methods

We identified 793 newly diagnosed HIV patients presenting to care at the CDC, the national infectious disease

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referral centre for Singapore, from a sentinel cohort. This sentinel sample is composed of randomly selected patients from 2006 to 2011, representing about 50% of HIV patients seen at CDC for care for the first time during this period; patients were selected using a random number generator. The inclusion criteria for selection were: (i) first visit for HIV infection was within 2006 to 2011, (ii) confirmed HIV diagnosis by ELISA and Western blot, (iii) Singapore citizen or permanent resident, and (iv) established follow-up care by having at least 1 entry in outpatient clinic notes. Overall, they comprised 30.5% of national cases. The sentinel sample is also used to audit our HIV programme as requested by the Ministry of Health, Singapore.

Demographic, clinical, laboratory, and outcome data (viral load suppression, hospitalisations, loss to follow-up, death) were retrospectively extracted from patient records by trained medical personnel. Gender, ethnicity, marital status and transmission risk factor information was based on patient self-report to the treating physician, as recorded in clinical charts. Hospitalisation history, CD4 count, HIV viral load and ART start date, and history of HIV opportunistic infections were obtained from electronic laboratory records and electronic inpatient discharge summaries. This study was approved by the Institutional Review Board, National Healthcare Group, Singapore [DSRB E/11/363].

An AIDS defining illness was defined using the 2008 United States Centers for Disease Control and Prevention guidelines.[8] The tuberculosis (TB) diagnosis was based on either a positive tuberculosis polymerase chain reaction test and/or isolation of *Mycobacterium tuberculosis* from a clinical specimen. Coinfection with hepatitis B or syphilis was based on a positive serology test for these pathogens.

The chi-square or Fisher's exact test was used to determine significance for categorical variables, and the Mann-Whitney U test was used for continuous variables. The Cuzick test for trend was used to make comparisons for continuous variables across years, and linear regression was used to determine significance of categorical variables across years. All tests were conducted at the 5% level of significance using Stata 12 (Stata Corp., College Station, TX).

Results

The demographic characteristics of the older and younger members of our cohort are shown in Table 1. There were 578 HIV patients who were less than 50 years of age and 215 patients who were aged 50 years and above. There were significantly more Chinese patients among those aged 50 years and above (88.4% versus 74.2%; P <0.001). The majority of the younger cohort was single (72.2%), while more of the older cohort was married (48.8%) or divorced, separated, or widowed (23.3%; P <0.001).

Table 1. Comparison of Demographic and Outcome Characteristics of HIV/AIDS Patients

Patients	<50 years old (n = 578)	≥50 years old (n = 215)	*P* value
Gender, male	538 (93.1)	204 (94.9)	0.323
Ethnicity			
Chinese	429 (74.2)	190 (88.4)	<0.001
Malay	98 (17.0)	13 (6.1)	
Indian	24 (4.2)	10 (4.7)	
Others	27 (4.7)	2 (0.9)	
Marital status			
Single	417 (72.2)	59 (27.4)	<0.001
Married	112 (19.4)	105 (48.8)	
Divorced/Separated/ Widowed	47 (8.1)	50 (23.3)	
Unknown	2 (0.4)	1 (0.5)	
Transmission risk			
Heterosexual	227 (39.3)	182 (84.7)	<0.001
Homosexual	255 (44.1)	12 (5.6)	
Bisexual	64 (11.1)	8 (3.7)	
Vertical transmission	1 (0.2)	0	
Injecting drug use	20 (3.5)	9 (4.2)	
Unknown	11 (1.9)	4 (1.9)	
Hospitalisation history			
Ever hospitalised	315 (54.5)	171 (79.5)	<0.001
Number of hospitalisations (median, IQR)	2 (1 to 3)	2 (1 to 4)	0.206
Outcome			
Lost to follow-up	82 (14.2)	27 (12.6)	0.525
Death	17 (2.9)	28 (13.0)	<0.001

All figures are represented as n (%) unless otherwise specified.
IQR: interquartile range

HIV acquisition risk was separated into mutually exclusive categories, as shown in Table 1. Most patients aged 50 years and above were heterosexual (84.7%), while more patients who were under 50 years of age were homosexual (44.1% versus 5.6% of the older cohort; P <0.001). One 16-year-old patient was seropositive since birth, and overall, 29 (3.7%) patients had histories of injecting drug use. Among single, younger patients, 252 (60.4%) were self-reported as homosexual, while among the older, married patients, 99 (94.3%) were heterosexual.

A greater proportion of older patients in our cohort were ever hospitalised (79.5% versus 54.5% of the younger cohort; P <0.001), although the number of hospitalisations for the 2 groups did not differ significantly. There was

no difference in the proportion of patients lost to follow-up, which we defined as the last visit more than 1 year ago (from the time of data extraction—17 April 2012). Thirteen percent of the patients aged 50 years and above died compared to 2.9% of the patients who were less than 50 years old (P <0.001).

Among younger patients, 389 (67.3%) presented with CD4 counts ≤350 cells/mm^3, compared to 184 (85.6%) of older patients (P <0.001; Table 2). More younger patients (57.4%) had most recent CD4 counts >350 cells/mm^3 compared to older patients (29.3%; P <0.001). The median time from clinical presentation to ART initiation was 49 days in the younger cohort, compared to 35 days in the older cohort (P = 0.008).

The majority of older patients were ever on ART (86.5% versus 76.5% of younger patients; P = 0.002). There was no difference in the proportion of patients who received Medifund (endowment fund from the Singapore government to help low income citizens pay for medication). Overall, 84.0% of our cohort had viral load tested. A greater proportion of older patients had viral load less than or equal to 200 copies/mL at their most recent test (81.7% versus 70.7% of younger patients; P = 0.004).

More of the older patients in our cohort were diagnosed with active TB (26.5% versus 11.6% of younger patients; P <0.001). The proportion of those who tested positive for hepatitis B or syphilis was not significantly different between the 2 groups, but more older patients suffered from at least 1 AIDS defining illness (66.5% versus 37.9% of younger patients; P <0.001).

Table 2. Comparison of Clinical Characteristics of HIV/AIDS Patients

Patients	<50 years old (n = 578)	≥50 years old (n = 215)	*P* value
CD4 count at presentation, cells/mm^3			
0 to 50	124 (21.6)	89 (41.8)	<0.001
51 to 199	122 (21.3)	66 (31.0)	
200 to 350	143 (25.0)	29 (13.6)	
351 to 500	105 (18.3)	20 (9.4)	
>500	79 (13.8)	9 (4.2)	
Most recent* CD4 count, cells/mm^3			
0 to 50	27 (4.7)	21 (9.9)	<0.001
51 to 199	67 (11.7)	72 (33.8)	
200 to 350	147 (25.7)	57 (26.8)	
351 to 500	174 (30.4)	35 (16.4)	
>500	158 (27.6)	28 (13.2)	
Antiretroviral therapy			
Median time from clinical presentation to ART start, days (IQR)	49 (18 to 294)	35 (14 to 102)	0.008
Ever on ART	442 (76.5)	186 (86.5)	0.002
Ever received Medifund for ART†	67 (15.3)	35 (19.7)	0.190
Viral load			
Ever tested	491 (85.0)	175 (81.4)	0.225
Most recent VL ≤200 copies/mL‡	347 (70.7)	143 (81.7)	0.004
Tuberculosis positive	67 (11.6)	57 (26.5)	<0.001
Hepatitis B positive	57 (9.9)	26 (12.1)	0.363
Syphilis positive	136 (23.5)	39 (18.1)	0.104
Diagnosed with AIDS defining illness	219 (37.9)	143 (66.5)	<0.001

All figures are represented as n (%) unless otherwise specified.
*As of 25 April 2012
†For those on ART
‡For those with VL ever done
ART: antiretroviral therapy
Medifund: an endowment fund from the Singapore government to help low income citizens pay for medication
VL: viral load

Conclusion

Patients with HIV aged 50 years and above comprised 27.1% of our sentinel cohort, presenting for clinical care at our institution with significantly lower CD4 T cell counts than their younger counterparts and experiencing greater mortality and morbidity in the form of hospitalisations, AIDS defining illnesses, and TB diagnoses. The initial low CD4 counts at clinical presentation and lower recovery of CD4 count may be due to slower immunological response in older patients.[9]

Interestingly, the number of hospitalisations did not differ significantly between older and younger patients despite more AIDS defining illnesses and deaths in the former group. Our data may not have captured all hospital episodes due to HIV infection since our older patients were diagnosed during the latter course of infection, as evidenced by their lower CD4 counts at diagnosis, compared to younger patients. Although comorbidity data were lacking, we could assume that older patients had more comorbid conditions,[10] but this did not lead to increased hospitalisations among older patients during the study period. However, we did not collect data on comorbidities or reasons for hospitalisation (HIV or non-HIV related) that might have influenced morbidity and mortality in our older patients. More of our patients aged 50 years and above had viral loads less than or equal to 200 copies/mL compared to those aged 50 years and below, possibly due to greater compliance to ART,[11] but we did not have detailed information on measures of adherence. Overall, 84% of patients had at least 1 viral load test that was performed.

Additionally, we only performed univariate analysis, as we did not have comprehensive data (e.g. patient comorbidities, infecting HIV subtype) that could have accounted for differences in CD4 counts between younger and older patients. Previously, we showed that patients infected with non-B subtype HIV had lower CD4 T cell counts pre- and 9 to 15 months post-ART, and more patients infected with non-B subtypes were heterosexual.[12] The reasons for the differences in clinical presentation between the 2 age groups may also be explained by socioeconomic status, educational status, or other sociological factors.

Marital status and transmission risk were strikingly different between our younger and older patients, although these data were self-reported. Prevention campaigns that highlight the need for early HIV testing are targeted towards the younger population in Singapore. The older population should also be targeted in such campaigns, which may be directed towards the at-risk primary care population as a whole.

The proportion of patients diagnosed with active TB was greater in the older age group, but given the limited data, we could not definitively conclude whether more patients were diagnosed after starting ART. Numerous studies have supported the theory of "unmasking TB"—when asymptomatic or mild TB is activated upon ART initiation. Additionally, TB risk decreases 10-fold with an increase in CD4 count from <100 cells/mm^3 to >500 cells/mm^3.[13] Thus it is not surprising that the older age group had more TB diagnoses because of their overall lower CD4 count at presentation.

Most studies looking at the consequences of late HIV presentation have been conducted in Western countries. Althoff et al[4] noted an increasing trend of older HIV patients over an 11-year study period in their North American cohort, and overall, 21% were aged 50 years and above. Older patients in a Swiss cohort presented with much higher CD4 counts (median 310 cells/mm^3 for those aged 50 to 64, 285 cells/mm^3 for those aged ≥65)[6] than those in our cohort (65 cells/mm^3 for those ≥50 years old). Combined data from 13 cohort studies in Europe and North America concluded that age is an independent predictor of clinical progression while on ART and that age 50 was the threshold for this effect.[14]

Despite the success of ART, there are many consequences of late HIV diagnosis, including a more complicated management strategy of concomitant diseases and opportunistic infections when starting treatment, as well as, from a public health perspective, ongoing transmission by individuals unaware that they are positive. The findings from our cohort indicate that public awareness should be increased among this growing age group in Singapore so that policymakers and healthcare providers can help facilitate earlier testing for older individuals at risk for HIV.

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