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Significant health impact of accelerated aging in young HIV-infected individuals on antiretroviral therapy in Malaysia.

Running title: Aging among treated HIV in Malaysia

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Abstract

Background: Aging among HIV-infected individuals on antiretroviral therapy (ART) is a significant clinical challenge however, studies assessing multidimensional aspects of aging are lacking. We characterised ten geriatric conditions (GCs) encompassing multiple functional domains, its health impact and associated risk factors in HIV-infected and age-matched uninfected controls.

Methods: HIV-infected individuals were recruited from the out-patient clinic in University Malaya Medical Centre, Malaysia and controls from the community. All participants were aged ≥25years, no acute illness and HIV-infected individuals were on stable ART. GCs were assessed and the burden scored as a composite of GCs present in an individual (total score=10). Multivariate regression analysis was performed to determine the risk factors and health impact associated with the burden of GCs.

Results: We analysed data from 336 HIV-infected individuals (total HIV+), of whom 172 were matched for age, gender and ethnicity with 172 HIV-uninfected controls (matched subset). In the total HIV+ cohort, median (interquartile range) age was 44(38-51)years and CD4 T-cell count was 562(398-737)cells/μl. The burden of GCs was significantly higher in the HIV-infected group compared to controls ($p<0.001$). With an increasing GC burden, quality of life scores were 2.2-times poorer, health-care utilisation 5-times greater and mortality risks scores 4-times higher in the HIV-infected group compared to matched controls. Both socio-behavioural and HIV-related clinical factors were independently associated with an increasing burden of GC in HIV.

Conclusions: A high burden of GCs with significant impact on health outcomes, including mortality risks scores are observed among HIV-infected individuals on ART in a resource-limited setting.

Keywords: Geriatric conditions, quality of life, aging, health outcomes, mortality risks scores, polypathology

Introduction

As life-expectancy increases with antiretroviral therapy (ART), age-related comorbidities now contribute to the main burden of disease associated with HIV infection[1]. Furthermore, these comorbidities have been reported to occur earlier among HIV-infected individuals compared to the general population[2, 3]. Geriatric syndromes which are conditions associated with functional deficits and typically measured in the elderly (>65 years)[4], were recently found to be prevalent even in middle-aged HIV-infected individuals[5, 6], suggesting that age-associated functional decline may occur independent of chronologic age in the HIV setting. These observations have led to the concept that HIV infection may accelerate or attenuate the biological aging process[7].

Aging in HIV infection is a multifactorial process involving the complex interplay of biological and non-biological constructs[8] and may differ depending on the socio-economic and geographic region studied[9]. HIV-related risk factors previously shown to be associated with age-related comorbidities including advanced immunodeficiency[10-13], prolonged immune activation and inflammation[14, 15], chronic co-infections[16, 17] and exposure to older and more toxic antiretroviral drugs[18], are all more prevalent in resource limited settings. Therefore, the presentation, burden and determinants associated with aging in HIV-infected individuals are likely to differ across various economic and cultural regions worldwide.

Most studies assessing the aging phenotype in the setting of HIV infection have largely focused on the accumulation of clinical comorbidities or polypathology as a manifestation of

aging[2, 3] while others have explored functional characteristics including frailty[11, 19] and cognitive impairment[20]. However, to date, only a single HIV center has assessed aging from a multidimensional perspective which encompasses both clinical and functional deficits[5, 6]. Findings from other regions including the developing country setting are lacking although these data are critical for planning healthcare resources and streamlining treatment strategies.

Thus, our study objectives were to 1) characterise a range of geriatric conditions among HIV-infected compared to age, gender and ethnically-matched HIV-uninfected controls in Malaysia; 2) explore how the burden of these conditions impacts health-related outcomes specifically quality of life, health care utilisation, mortality risks scores and self-rated health; and 3) determine the socio-behavioural and clinical risk factors associated with the burden of geriatric conditions among HIV-infected individuals in our setting.

Methodology

Study population

The Malaysian HIV and Aging (MHIVA) study was established to characterise the extent of geriatric health issues experienced by individuals undergoing routine HIV care through the HIV Clinic in University Malaya Medical Centre (UMMC), Malaysia. The clinic provides ambulatory care to approximately 1100 patients in the urban Klang Valley. All registered patients were invited to participate in the study during their routine follow-up if they fulfilled the following criteria; age ≥ 25 years, on stable ART (HIV RNA <50 copies/mL for at least 12 months), not pregnant and no acute illness at recruitment. HIV-uninfected controls of the same age range were recruited among accompanying friends of the HIV-infected participants, hospital staff volunteers and among community-dwelling individuals responding to study fliers distributed in the hospital catchment area. All controls consented to a rapid HIV

screening test (Alere HIV Combo, Chiba, Japan) prior to enrolment. Consenting participants subsequently attended a research clinic where they answered a structured questionnaire and had clinical assessments performed by trained personnel. All assessments including biochemical screening were completed at two consecutive clinic visits scheduled within 6 months. All participants provided informed consent and the study protocol was approved by the institutional review board (MEC 20151-937).

Data collection

Participants answered a questionnaire (assisted when needed) pertaining to demographics, socio-behavioral and health information. All medications (prescribed and over-the- counter) including health supplements were recorded. All HIV-related information was verified through hospital records. Biochemical screening included fasting glucose and lipids, HbA1c, insulin levels, renal function test, liver function test, thyroid function, complete blood count, high sensitive C-reactive protein, D-dimer, hepatitis B, C and CMV serology, screening for syphilis, HIV RNA and CD4/CD8 T-cell counts.

Assessment of geriatric conditions

The GCs assessed in this study involved several domains; gait/balance abnormalities, malnourishment, frailty, visual impairment, urinary incontinence, polypathology, polypharmacy, depression, cognitive impairment and functional disability. The range of geriatric conditions (GCs) selected were based on the following consideration; 1) conditions from literature searches previously shown to have an impact on health outcomes in the general population in the region[21-26] and among HIV-infected individuals[2, 5, 13, 27-30] and 2) conditions with tools previously utilised among the Asian population in the outpatient

clinic setting[31-34]. Although our study population was younger than the typical elderly (>65 years), we utilised standard tools developed for the elderly population as done in prior studies[5, 35]. The definitions and cut-offs used for each of these conditions are shown in Supplementary Table 1, http://links.lww.com/QAD/B71.

Assessment of health-related outcomes

Health outcomes assessed included the number of visits to any healthcare facility in the past 12 months as an indicator of healthcare utilisation; quality of life (QoL) scores which assessed the domains of control, autonomy, self-realisation and pleasure (CASP-12)[36] and self-rated health which was measured by asking participants to rate their health on a scale of 1 to 5 corresponding to poor, fair, good, very good and excellent. The VACS (Veterans Aging Cohort Study) index, an established surrogate for mortality risks ~~in HIV-infected[37] and uninfected individuals[38]~~ was also computed by adding points for components of age, HIV RNA, haemoglobin levels, CD4 T-cell counts, hepatitis C, estimated glomerular filtration rate (eGFR) and Fibrosis Index-4 (FIB-4) as previously described in the HIV-infected[37] and by assigning 0 points for CD4 T-cell count and HIV RNA using the same formula for the uninfected individuals[38].

Statistical analysis

Graphical, multicollinearity and heteroscedasticity tests were used to assess the appropriateness of the data for the models. The burden of geriatric conditions was assessed as a composite of the total number of GCs present in an individual as an ordinal score (range 0-10)[39]. Multivariate linear and ordered logistic regression was used to assess the impact of the burden of GCs on health-outcomes while Poisson regression analysis using robust

standard errors for parameter estimates was performed to identify risk factors associated with the burden of GCs. Variables that had an influence in the univariate analysis at a level of $p<0.200$ were included in the final multivariate model. All statistical analyses were performed using Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX). Statistical significance for covariates and interactions were defined as $p<0.050$ and all models are presented adjusted for significant interactions which are annotated.

Results

Characteristics of the study population

Data from 336 HIV-infected and 299 HIV-uninfected individuals were complete and available for analysis at the end of enrolment in June 2016. For this study, data from all 336 HIV-infected individuals (herein called the total HIV+) were analyzed. For comparisons with HIV-uninfected controls, participants from both groups were matched to the closest ± 1 year of age, gender and ethnicity and 172 pairs were identified for analysis (herein called the matched subset). The subset of 172 matched HIV-infected individuals was not significantly different from the total HIV+ cohort in terms of demographics, socio-behavioral and HIV-related characteristics (Table 1 and Supplementary Table 2, http://links.lww.com/QAD/B71).

Among the total HIV+ cohort, the majority were males (83%) and ethnic Chinese (71%) with a median (interquartile range, IQR) age of 44 (38-51) years and CD4 T-cell count of 562 (398-737) cells/μl (Table 1). The median (IQR) treatment duration was 6 (3-10) years and 55% reported heterosexual transmission. 44% reported a history of AIDS-defining illness and the median (IQR) baseline CD4 T-cell count was 111 (36-246) cells/μl (Supplementary Table 2, http://links.lww.com/QAD/B71).

In the matched subset, education levels were significantly different with more individuals reporting tertiary education among the controls compared to HIV-infected (63% vs 45%, p<0.001). Smoking status and alcohol consumption were significantly different with more controls reporting never smoking (80% vs 60%, p<0.001) and never drinking (51% vs 45%, p=0.001) while physical activity was comparable in both groups (p=0.852). Although fewer HIV-infected individuals were either overweight or obese (28% vs 46%, p=0.001), a greater proportion exhibited intra-abdominal obesity compared to controls (53% vs 40%, p=0.017). Significantly fewer controls also reported cardiovascular (43% vs 60%, p=0.001), endocrine (10% vs 22%, p=0.002) and gastrointestinal disorders (6% vs 12%, p=0.038) compared to HIV-infected participants (details listed in the footnotes of Table 1).

Prevalence of geriatric conditions

Ten multidimensional GCs were assessed in all participants. In the matched subset, the prevalence of GCs was numerically higher in the HIV-infected compared to controls for all assessments (Fig 1A); with cognitive impairment, depression, polypathology and polypharmacy statistically different in both groups. The median (IQR) number of GCs among HIV-infected were 2 (1-3) compared to 1 (0-2) in uninfected controls (p=0.0176) while the proportion of individuals with one or more GCs were significantly higher among HIV-infected compared to controls, 88% vs 63%, p<0.001. When assessed by age categories, there was a higher frequency of multiple GCs present (two or more conditions) in all age groups in the HIV-infected compared to matched controls (Fig 1B). Using univariate Poisson regression, the burden of GCs was significantly lower in the uninfected group compared to HIV-infected individuals (IRR=0.65, 95%CI=0.54-0.79; p<0.001) and remained significant after adjusting for traditional factors associated with aging including smoking, alcohol, education and employment in addition to age, gender and ethnicity (IRR=0.72, 95%CI=0.60-

0.85; p<0.001). The prevalence of GCs when assessed in the total HIV+ cohort (n=336) was comparable to that in the HIV-infected arm of the matched subset (data not shown).

Health outcomes associated with the burden of geriatric conditions

We next assessed the impact of the burden of GCs on health outcomes in the total HIV+ cohort. All the health outcomes assessed including quality of life, mortality risks scores, healthcare utilization and self-rated health were significantly associated with an increasing burden of GCs after adjusting for age, gender and ethnicity and testing for interactions (Supplementary table 3, http://links.lww.com/QAD/B71). Subsequently, we assessed if this impact was different in the HIV-infected and uninfected individuals by including a group variable in the analysis. We found that quality of life scores in the HIV uninfected individuals were 2.2 times higher compared to HIV-infected individuals (ß-coefficient (95%CI) =2.16 (0.98 – 3.35), p<0.001) (Fig 2A) with an increasing burden of GCs. Healthcare utilization was 4.9 times less in the HIV uninfected compared to HIV-infected individuals with the accumulation of GCs (ß-coefficient (95%CI) =-4.88 (-5.77 - -3.91), p<0.001) (Fig 2B). Mortality risks scores were also increased with an increased burden of GC but to a lesser extent in the HIV uninfected compared to HIV-infected (ß-coefficient (95%CI) =-4.03 (-6.13 – -1.93), p<0.001) (Fig 2C). Finally, although self-rated health declined significantly with increased burden of GC in both groups, its impact was not different when comparing HIV-infected and uninfected individuals (ß-coefficient (95%CI) =0.22 (-0.22 – 0.65) p=0.332 (Fig 2D).

Risk factors associated with an increasing burden of geriatric conditions in HIV-infected individuals

In the analysis of risk factors associated with GCs in the total HIV+ cohort (Table 2), we found increasing age (IRR=1.01, 95%CI=1.00-1.02; *p*=0.046) and ethnic Chinese and Indians (IRR=0.99, 95%CI=0.80-1.24 and IRR 1.44, 1.09-1.88; *p*=0.017) vs Malays were associated with the burden of GCs. As expected, lower education attainment (primary vs secondary and tertiary; IRR=0.62, 95%CI=0.85-1.27 and IRR=0.78, 95%CI=0.58-0.86; *p*=0.034), unemployment (IRR=0.71, 95%CI=0.58-0.86; *p*=0.001) and low physical activity (IRR=1.25, 95%CI=1.08-1.46; *p=0.004*) were all both associated with an increased burden of GCs. Additionally, employment (IRR=0.71, 95%CI=0.58-0.86; *p*=0.001) was associated with a lower burden of GCs. There was also an association between increased intra-abdominal obesity (IRR=7.09, 95%CI=1.44-35.01; *p=0.016*) and social isolation (IRR=11.11, 95%CI=1.44-76.5; *p*=0.015) with the burden of GCs and a strong interaction between these variables. Unexpectedly, previous alcohol consumption was associated with an increased burden of GCs while current consumption was associated with a reduced burden (previous and current consumption vs never; IRR=1.04, 95%CI=0.85-1.27 and IRR=0.80, 95%CI=0.42-0.96, p=0.017). Among the HIV-related clinical factors, only lower CD4:CD8 ratio (IRR=0.02, 95%CI=0.43-0.93; *p*=0.016) and a history of ADI (IRR=1.19, 95%CI=1.01-1.39; *p*=0.036) were significantly associated with an increased burden of GCs.

Discussion

To our knowledge, this is the first study to systematically assess and compare the multidimensional aspects of aging and its health impact among HIV-infected and uninfected individuals in the Asian setting. Of significant clinical implications, we found a higher burden of GCs in a largely young cohort of HIV-infected individuals with well controlled disease compared to demographically-matched uninfected controls. There was also a high prevalence of multiple GCs co-occurring in all the age groups assessed within the HIV-

infected cohort. An increased burden of GCs was associated with more adverse health outcomes in the HIV cohort compared to uninfected controls. This study highlights the impact of both socio-behavioral and HIV-related clinical factors on the burden of GCs in a resource-limited setting.

Limited studies have examined aging in the setting of HIV as a multidimensional construct and all of them have focused on middle-aged or older individuals living in developed countries[5, 6]. This study was uniquely designed to identify GCs in young HIV-infected patients. We rationalized that the age cut-offs traditionally used in studies assessing geriatric issues in HIV-infected individuals may be less relevant in the developing country setting given that many of the determinants of GCs including persistent immune activation, social isolation, substance abuse and low physical activity are not age-specific issues. Our findings clearly show that multiple GCs occur more frequently among HIV-infected individuals aged in their 30s and 40s compared to uninfected controls, suggesting that the occurrence of GCs in the HIV population is more prevalent than previously described[5, 6, 11, 12, 14, 40]. This highlights a degree of medical complexity not previously described among non-elderly treated HIV-infected individuals and warrants further attention.

The implications of GCs in treated HIV-infected individuals, particularly among younger individuals have not been well studied. As in the elderly[41], the accumulation of GCs in this predominantly young HIV-infected cohort were associated with poor prognosis, namely increased healthcare utilization, increased mortality risks scores, poorer quality of life and self-rated health scores. The presence of GCs in young adults may not be classically viewed intrinsically as a geriatric issue and in the HIV-infected may be driven by different

pathophysiologic processes compared to the uninfected. Nevertheless, our findings suggest that its occurrence may similarly imply a state of vulnerability and a potential inability to deal with increasing life challenges which is conceptually similar to the consequence of these conditions when present in the elderly[4]. Of significance, we found that the burden of GCs had a more adverse impact on health outcomes in the HIV-infected compared to uninfected controls, implying a greater vulnerability to age-associated conditions among the HIV-infected in our setting. People living with HIV in less developed countries may experience greater constraints in economic and social resources due to issues such as job instability, fragile social networks, stigma and discrimination which may complicate the natural aging process-physically, emotionally, and socially[8]. Similar adverse interactions between HIV and aging has previously been described but among older individuals[30]. Our findings suggest that these issues are evident even in younger HIV-infected individuals.

We found that depressive symptoms and lower performance in cognitive function were highly prevalent in our HIV cohort similar to previous reports[42-44]. The higher frequency of polypathology among the HIV-infected cohort compared to controls were largely driven by an increased prevalence of cardio-metabolic disorders, consistent with previous studies[1-3]. There were large differences in the prevalence of polypharmacy in the HIV-infected and uninfected groups. Even when only non-antiretroviral medications were considered, the median number of medications taken by HIV-infected individuals remained significantly higher compared to controls (p=0.010). Health supplements contributed significantly to polypharmacy in our setting with 33% of the HIV-infected and 28% of the uninfected reporting the intake of one or more supplements (data not shown). Significant drug-drug interactions between ART and health supplements have previously been reported[45] and these may potentially contribute to complications such as delirium, falls and hospitalization;

and warrants further study in our setting. All the other GCs assessed were numerically higher in the HIV-infected compared to uninfected controls and consistent with prior reports[46-49]. The proportion of HIV-infected individuals presenting with two or more GCs in this cohort was comparable to the prevalence reported in individuals almost 14 years older in the developed country setting[5]. However, no study to date has compared aging using multidimensional geriatric assessments between HIV-infected and matched controls.

The socio-behavioral factors associated with aging in the total HIV+ cohort were generally similar to factors previously described in population-based studies in our region[21, 22]. These include ethnic-associated differences with the Chinese having a lower risk of an increased burden of GCs compared to ethnic Malays and Indians, while unemployment, lower education status and increasing age were all associated with an increased burden of GCs.

Low physical activity was independently associated with an increased burden of GCs as previously described[22]. The strong interaction between intra-abdominal obesity and social isolation found in our study implied that individuals with increased intra-abdominal obesity were also those most likely to report being socially isolated with a high burden of GCs. Multiple dimensions of poor health in HIV-infected individuals may stem from low physical activity including reduced physical function[29], increased depression[42, 50], poor cognitive function[51] and increased cardiometabolic risks[52, 53]. Interventions to improve physical fitness even with moderate levels of exercise were found to improve all of these domains in older HIV-infected individuals[54]. One third of our cohort reported low physical activity

similar to other HIV cohorts[52] and thus identifies a group where a directed exercise program may help attenuate further functional decline.

Current CD4 T-cell counts were not associated with the burden of GCs as suggested in previous findings[11, 13]. Instead, we found an association with low CD4:CD8 ratio, extending the list of outcomes previously associated with this marker. Lower CD4:CD8 ratio have been associated with serious non-AIDS events and mortality among treated HIV-infected individuals[55-57] and predictive of an "inflammaging" phenotype[58]. It is currently unclear if similar immunological derangements are associated with the burden of GC in our cohort though hsCRP was no longer significant in the multivariate model after adjusting for traditional lifestyle-related factors. A history of AIDS-defining illness (ADI) was also independently associated with the burden of GCs in our study. This is consistent with a prior study which found a history of advanced immunodeficiency as reflected by a low CD4 T-cell nadir to be associated with an increased burden of GCs[5] among middle-aged HIV-infected individuals.

There were several unexpected findings in our study. Surprisingly smoking status was not associated with the burden of GCs as previously suggested[8, 59]. Additionally, we found current alcohol consumption was associated with a lower burden of GC compared to those who never drank while past consumption was associated with an increased burden. The reasons for these are currently unclear but may be associated with differences in the amount of alcohol and tobacco consumed as highlighted in a recent review[60], and the associated ethnic bias in substance abuse, details which were not quantified reliably in our study.

Without these details, we find it hard to speculate potential reasons for our findings and suggest further studies be conducted to verify these associations.

The major strength of our study is the comparative assessment of multiple geriatric conditions and health-related outcomes in a large cohort of HIV-infected to age, gender and ethnically-matched controls. This allowed for a more accurate approximation of the aging phenotype in HIV and its implications. Of note, the operational definition used in this study to measure the burden of GCs correlated well with health outcomes previously shown to be important for successful aging in the general population[21, 22, 61]. Thus, the burden of GCs measured as a composite of multidimensional geriatric assessments may be a useful interim outcome to reflect the complications of aging in HIV when longitudinal mortality data are not available. There were however, several important limitations too. Firstly, our inclusion criteria which focused on virologically suppressed individuals would have inadvertently excluded individuals who may have been experiencing issues with ART adherence as a result of difficulty in taking medications (IADL), depression or polypharmacy. We however chose to focus the study on individuals with well controlled HIV disease so as to be able to better capture the incremental issues associated with HIV in a setting where virologic control was no longer a problem. Secondly, our study was a cross-sectional study and we cannot infer causality for the associations found. Thirdly, our study was conducted in a single HIV centre in an urban setting in Malaysia and thus our findings are not generalizable to HIV-infected individuals living in rural settings. Finally, we did not assess recreational drug use in our cohort which has been previously associated with increased burden of GCs[39]. Substance abuse has historically been associated with punitive actions in our setting and disclosure of its use even to healthcare professionals is highly unreliable.

In conclusion, we found a high prevalence of multiple GCs among ART treated HIV-infected individuals compared to demographically-matched uninfected controls, most of whom were <50 years and living in a resource-limited setting. The accumulation of GCs was associated with poorer health-related outcomes in the HIV-infected group compared to uninfected controls. Some of the socio-behavioral risk factors associated with the burden of GCs in HIV-infected individual including low physical activity, social isolation, increased intra-abdominal obesity and unemployment are modifiable and offer an immediate opportunity for intervention to attenuate further functional decline. The association of low CD4:CD8 ratio and a history of ADI with increased burden of GCs affirms the need to initiate HIV treatment early. It is evident that a multi-disciplinary team approach and an emphasis on monitoring of risks should be considered to meet the complex care needs of HIV-infected individuals. Overall, our findings highlight the need to extend the focus of HIV care beyond treatment targets of immunological and virological outcomes.

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Conflict of interest

The authors declare no commercial or financial conflict of interest.

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Table 1: Comparison of patient characteristics in the whole HIV+ cohort (n=336) and the subset of HIV+ with age, gender, ethnically-matched HIV uninfected controls (n=172 pairs).

Characteristics	Total HIV+	Matched HIV+	Matched HIV-negative	*P*-value*
Total	336	172	172	
Age, years	43.6 (37.5-51.0)	42.4 (33.8-0 52.1	42.4 (34.3 – 52.6)	0.598
Gender, n(%)				1.000
Male	278 (82.7%)	126 (73.3%)	126 (73.3%)	
Female	58 (17.3%)	46 (26.7%)	46 (26.7%)	
Ethnicity, n(%)				1.000
Malay	63 (18.8%)	41 (23.8%)	41 (23.8%)	
Chinese	240 (71.4%)	114 (66.3%)	114 (66.3%)	
Indian	33 (9.8%)	17 (9.9%)	17 (9.9%)	
Highest education level, n(%)				<0.001
Primary or less	50 (14.9%)	31 (18.0%)	8 (4.7%)	
Secondary	115 (34.2%)	49 (28.5%)	55 (32.0%)	
Tertiary	171 (50.9%)	92 (45.8%)	109 (63.4%)	
Currently employed, n(%)	282 (85.2%)	134 (78.8%)	137 (81.1%)	0.606

Current CD4 T-cell count, cells/μl	562 (398-737)	547 (399 – 744)	-	
Current CD4:CD8 ratio	0.63 (0.43-0.89)	0.62 (0.42 – 0.84)	-	
Prior exposure to ddI/ddC/d4T/AZT, n(%)	252 (75.0%)	121 (70.4%)	-	
History of AIDS defining illness, n(%)	147 (43.8%)	71 (41.3%)	-	
Hepatitis B surface antigen positive, n(%)	14 (4.2%)	7 (4.1%)	5 (3.0%)	0.585
Hepatitis C antibody positive, n(%)	8 (2.4%)	5 (2.9%)	1 (0.6%)	0.104
CMV IgG levels, IU/ml	444 (201-500)	440 (171-500)	159 (40 – 495)	<0.001
Highly-sensitive C-reactive protein, mg/L	1.6 (0.4-4.8)	1.35 (0.4 – 4.6)	0.8 (0.2 – 3.4)	0.038
Comorbidities present[†], n(%)				
Cardiovascular	280 (92.4%)	103 (60.2%)	74 (43.0%)	0.001
Endocrine	62 (18.5%)	38 (22.1%)	17 (9.9%)	0.002

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Musculoskeletal	21 (6.3%)	15 (8.7%)	13 (7.6%)	0.693
Ophthalmic	27 (8.2%)	17 (10.1%)	12 (7.0%)	0.308
Urology	32 (9.5%)	18 (10.5%)	14 (8.1%)	0.458
Respiratory	34 (10.2%)	17 (9.9%)	10 (5.8%)	0.161
Oncologic	9 (2.7%)	6 (3.5%)	4 (2.3%)	0.521
Gastrointestinal	23 (6.9%)	21 (12.2%)	10 (5.8%)	0.038
Renal	5 (1.5%)	1 (0.6%)	1 (0.6%)	#
Neurologic	4 (1.2%)	3 (1.7%)	1 (0.6%)	#
Psychiatric	30 (9.0%)	17 (9.9%)	8 (4.7%)	0.062
Number of comorbidities	2 (1-3)	2 (1-3)	2 (1-2)	0.300
Number of medications	4 (3-6)	4 (3-6)	1 (0-2)	<0.001
Smoking status, n(%)				<0.001
	181 (54.7%)	100 (59.2%)	137 (79.7%)	
Never	52 (15.7%)	25 (14.8%)	12 (7.0%)	
Previous	98 (29.6%)	44 (26.0%)	23 (13.4%)	
Current				
Alcohol consumption, n(%)				0.001
	124 (37.2%)	77 (45.0%)	87 (51.2%)	
Never	59 (17.7%)	26 (15.2%)	6 (3.5%)	
Previous	150 (45.1%)	68 (39.8%)	77 (45.3%)	
Current				

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Low physical activity, n (%) (IPAQ, <600MET-minutes/week)	107 (31.9%)	62 (36.1%)	60 (34.9%)	0.852
Body mass index, kg/m^2				0.001
Underweight (<18.5)	34 (10.1%)	20 (11.6%)	8 (4.7%)	
Normal (18.5 - <25)	201 (59.8%)	104 (60.5%)	85 (49.4%)	
Overweight (25 - <30)	82 (24.4%)	39 (22.7%)	55 (32.0%)	
Obese (≥ 30)	19 (5.7%)	9 (5.2%)	24 (14.0%)	
Intra-abdominal obesity, n (%) (Waist-hip ratio <0.90 males; <0.85 females)	167 (49.7%)	91 (52.9%)	69 (40.1%)	0.017
Socially isolated, n (%) (LSNS-6 score <12)	139 (42.4%)	75 (44.9%)	49 (28.6%)	0.002
Quality of life (QoL), CASP-12 score	24 (20-28)	24 (19 – 28)	28 (23 – 31)	<0.001
Number of visits to a	6 (4-9)	7 (5 – 10)	1 (0-3)	<0.001

healthcare facility in the last 12 months				
VACS index score	6 (0-16.5)	10 (0-22)	5.5 (0-12)	0.002
Number of geriatric conditions (GCs)	2 (1-3)	2 (1-3)	0 (1-2)	<0.001
Presence of 1 or more GCs, n (%)	287 (85.4%)	151 (87.8%)	109 (63.4%)	<0.001
Presence of 2 or more GCs, n (%)	180 (53.6%)	100 (58.1%)	50 (29.1%)	<0.001

Abbreviations: ddI-didanosine; ddc-zalcitabine; d4T- stavudine; AZT-zidovudine; MSM-men who have sex with men; IDU-injecting drug users; VACS – Veterans Aging Cohort Study; IPAQ – International Physical Activity Questionnaire; CASP-12 - Control, Autonomy, Self-realisation and Pleasure-12 scale; LSNS-6-Lubben Social Network Scale-6; MET-minutes/week – metabolic minutes per week which is calculated as multiples of metabolic rate (according to type of activity: vigorous, moderate or walk) multiplied by duration of performed activity within a week.

*P-values indicate differences between the matched HIV-infected and uninfected group; # Numbers within each group too small to make a meaningful comparison; †Cardiovascular diseases included myocardial infarction, ischemic heart disease, hypertension, hyperlipidemia, congestive heart failure, arrhythmia, stroke, transient ischemic attack, peripheral vascular disease; Endocrine diseases included diabetes mellitus, thyroid disease, impaired fasting glucose; musculoskeletal diseases included osteoarthritis, gout; ophthalmic disorders included glaucoma and macular degeneration; Urologic diseases included benign prostatic hypertrophy and all other conditions excluding urinary incontinence; Respiratory diseases included asthma, bronchitis and chronic obstructive pulmonary disease; Oncologic diseases included all malignancies; Gastrointestinal diseases included liver disease, peptic/duodenal ulcers, gastroesophageal reflux disease; renal disease included chronic kidney disease independent of dialysis requirement; Neurologic disorders included seizures, dementia and Parkinsons; Psychiatric diseases included clinical depression and psychosis.

Table 2: Factors associated with the burden of geriatric conditions

Variables	Univariate analysis		Multivariate analysis[#]	
	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value
Age, years	1.02 (1.01 – 1.03)	*<0.001*	1.01(1.00 – 1.02)	**0.046**
Ethnicity		*0.006*		**0.017**
Malay	Ref		Ref	
Chinese	0.99 (0.81 – 1.21)		0.99 (0.80 – 1.24)	
Indian	1.48 (1.11 – 1.98)		1.44(1.09 – 1.88)	
Gender		*0.029*		0.182
Male	Ref		Ref	
Female	1.27 (1.03 – 1.57)		1.34 (0.87 – 2.04)	
Socio-behavioral factors				
Education		*0.001*		**0.034**
Primary or below	Ref		Ref	
Secondary	0.71 (0.57 – 0.90)		0.62 (0.85 – 1.27)	
Tertiary	0.63 (0.51 – 0.79)		0.78 (0.54 – 1.13)	
Employment	0.56 (0.46 – 0.69)	*<0.001*	0.71 (0.58 – 0.86)	**0.001**
Alcohol consumption		*0.001*		**0.017**
Never	Ref		Ref	

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Previous	1.02 (0.81 – 1.28)		1.04 (0.85 – 1.27)	
Current	0.73 (0.62 – 0.88)		0.80 (0.42 – 0.96)	
Smoking status		0.633	-	-
Never	Ref		-	-
Previous	0.95 (0.77 – 1.19)		-	-
Current	0.91 (0.75 – 1.11)		-	-
Low physical activity	1.41 (1.20 - 1.67)	*<0.001*	1.25 (1.08 – 1.46)	**0.004**
Intra-abdominal obesity	6.36 (1.85 – 21.9)	*0.003*	7.09 (1.44 – 35.01)	**0.016**
Social isolation		*0.049*		**0.015**
No	Ref		Ref	
Yes	1.18 (1.00 – 1.40)		11.11 (1.61 – 76.5)	
Clinical factors				
Baseline CD4 T-cell counts, cells/µl	1.00 (1.00 -1.00)	0.594	-	-
Current CD4 T-cell counts, cells/µl	1.00 (1.00 -1.00)	0.548	-	-
Current CD4:CD8 ratio, per unit	0.85 (0.67 – 1.06)	*0.143*	0.02(0.43 – 0.93)	**0.016**
Duration on ART, years	1.00 (1.00 -1.00)	0.191	1.00 (0.99 – 1.00)	0.525
History of ADI		*0.003*		**0.036**

No	Ref		Ref	
Yes	1.28 (1.09 – 1.51)		1.19 (1.01 – 1.39)	
hsCRP, mg/L	1.01 (1.00 – 1.02)	*0.037*	1.01 (1.00 – 1.02)	0.333
Prior exposure to ddI/ddC/d4T/AZT		*0.079*		0.267
No	Ref		Ref	
Yes	1.20 (1.00 – 1.47)		1.19 (1.01 – 1.39)	

#adjusted for all variables with p<0.20 in the univariate analysis and denoted in *italics.* Interactions included were between, CD4:CD8 ratio and Gender, Social Isolation and Education and between Social Isolation and WHR and Gender.

Abbreviations: ADI-AIDS-defining illness; hsCRP-high-sensitivity C-reactive protein; ddI-didanosine, ddC-zalcitabine; d4T-stavudine; AZT-zidovudine; ART-antiretroviral therapy.

Figure 1: Prevalence of specific geriatric conditions (GCs) and the distribution of the number of GCs by age groups in HIV-infected individuals on suppressive ART and age, gender and ethnically-matched uninfected individuals

The bar graphs show (A) the comparison in prevalence of all the geriatric conditions assessed in this study and (B) the distribution of the number of GCs present (0, 1 ,2 and ≥3) by age categories in the subset of HIV-infected individuals (n=172) with age, gender and ethnically-matched uninfected controls (n=172) in the cohort. *represents comparisons which were significantly different ($p<0.001$) in the 2 groups when assessed by McNemars test. Abbreviations: MOCA-Montreal Cognitive Assessment; DASS 21-Depression, Anxiety and Stress Scale; IADL-Instrumental activities of daily living.

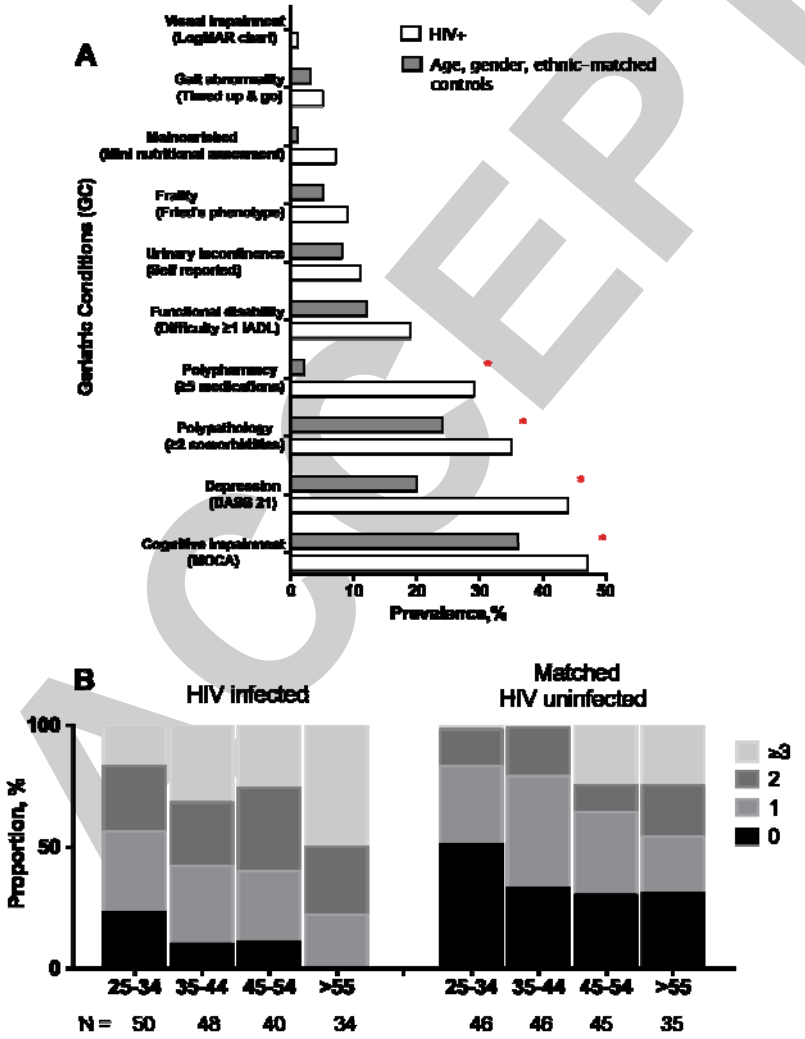

Figure 2: Association between health outcomes and increasing burden of geriatric conditions (GCs) in HIV-infected and age, gender, ethnically-matched HIV uninfected individuals.

The box and whisker plot shows the changes in (A) median quality of life scores (QOL, CASP-12), (B) median number of hospital visits in the last 12 months (healthcare utilization), (C) median VACS index scores, as a marker of mortality risks and (D) median self-rated health scores in individuals with an increasing burden of geriatric conditions. P-values indicate statistical significance for comparative group associations between health outcomes and an increasing burden of GCs in the HIV-infected and uninfected individuals using multivariate regression following adjustments for age, gender and ethnicity.