Immune recovery of middle-aged HIV patients following antiretroviral therapy
An observational cohort study

Ngai Sze Wong, PhD[a], Kenny Chi Wai Chan, FRCP[b], Edward Ka Hin Cheung, MPH[a], Ka Hing Wong, FRCP[b], Shui Shan Lee, MD[a,*]

Abstract

In HIV-infected persons, age is negatively associated with optimal CD4 recovery following antiretroviral therapy. Our understanding of the situation in older adults, especially the middle-aged is, however, limited. We undertook to examine the latter's pattern of CD4/CD8 recovery following antiretroviral therapy.

Retrospective clinical cohort data of HIV patients diagnosed between 1985 and 2014 in Hong Kong were collected. They were categorized by age at treatment initiation, viz., young adults (age 18–49), middle-aged (age 50–64), and elderly (≥65 years' old). Predictors of immune recovery (CD4 count, CD8 count, CD4/CD8 ratio) over time were examined using multivariable linear generalized estimating equations.

A total of 2754 patients (aged ≥18) have been on antiretroviral therapy, with baseline characteristics similar between middle-aged and the elderly. Late diagnosis, defined as progression to AIDS within 3 months of HIV diagnosis, was less common in middle-aged (odds ratio = 0.58, 95% confidence interval = 0.37–0.91). Among Chinese patients who have been on treatment for ≥4 years (n = 913), 80.6%, 14.6%, and 4.8% were young adults, middle-aged, and elderly respectively. Late treatment initiation, defined as AIDS diagnosis or CD4 count ≤100 cells/μL before treatment, was common in middle-aged and elderly, the former however had faster CD4 recovery (3.95 vs. 3.36 cells/μL/month), but slower CD8 decline (−1.76 vs. −4.34 cells/μL/month) and CD4/CD8 normalization (0.009 vs. 0.0101/month).

As a transitional age group, the immune recovery of middle-aged patients lagged behind young adults largely because of late treatment initiation. Following adoption of early and non-CD4-guided treatment initiation, their long-term clinical outcome is expected to improve.

Abbreviations: CMV = Cytomegalovirus, GEE = generalized estimating equations, HAART = highly active antiretroviral therapy, IDU = injection drug use, IQR = interquartile range, NNRTI = non-nucleoside reverse-transcriptase inhibitors, NVP = nevirapine, OR = crude odds ratio.

Keywords: ageing, HIV, immunity, lymphocyte

1. Introduction

Clinically, age is an important predictor of clinical outcome after antiretroviral therapy in HIV patients, as observed in a number of studies.[1,2] Compared with younger patients, older adults had poorer CD4 recovery after highly active antiretroviral therapy (HAART) initiation, higher mortality and co-morbidity rate.[3,4]

However, owing to poor retention in care in young patients, the risk of viral rebound, virological failure, and immunological failure was higher in younger than older patients.[1,5] It is clear that the final clinical outcome is dependent not just on the rate and extent of one's immunological recovery, but also on factors associated with good adherence to and tolerability of prescribed

HAART regimens. Their associations with clinical outcomes are both age-dependent.[1,3–5] As HAART is lifelong treatment, an increasing proportion of older adults is anticipated to be on treatment in the coming years. This poses a challenge in the monitoring of immunological outcome of patients across all ages, as attention may be needed on factors, which are age-associated.

As a sexually acquired infection, HIV affects largely sexually active young adults at the time of virus transmission. Since there's often a time lag between infection and diagnosis, and from diagnosis and to treatment initiation, a proportion of HIV-infected young adults might have entered their middle age when therapy begins. Arbitrarily defining "middle-age" as the age band between 50 and 64 years, these persons constitute a unique group transiting from young to old. Their immune outcome might be affected by a mix of factors related to both younger and older-aged individuals, including poor retention in care rate,[1] delayed HIV diagnosis,[6] aging[7] and other factors. In previous studies, patients were conventionally categorized with a cut-off of 50, 55, and 60 years for the elderly, whereas middle-aged group was subsumed under either younger- or older-aged category. A study in South Africa compared adults aged 25 to 54 and aged ≥55 years, revealing that patients aged ≥55 years had lower CD4 recovery rate 6 months after HAART initiation, even though they had better viral suppression.[1] Another study has included 50- to 59 years old and ≥60 years old as 2 of 5 age groups, showing positive association between age at HAART initiation and poor clinical outcomes and mortality.[7] In either circumstance, however, the immune outcome of middle-aged HIV patients has not been specifically addressed.

In planning this study, we hypothesized that middle-aged HIV patients constitute a distinct group whose immunological recovery following HAART could outperform the elderly despite their similar baseline characteristics, on the ground that they could benefit from earlier treatment initiation, comparable to the younger patients. As older patients were more likely to be late for treatment,[8] early initiation of HAART for the middle-aged would advance their treatment start-date to match with that of young adults, whose immunological recovery should be superior to the other 2 groups. To prove this hypothesis, we examined the immune recovery of middle-aged HIV patients in a clinical cohort in Hong Kong, where standard HAART regimens have been offered in accordance with established protocols. They were compared with young adults and the elderly followed up under the same protocols. We used 3 markers—CD4, CD8, and CD4/CD8 ratio—to study the immunological change after HAART initiation, and examine their associations with the timing of treatment initiation.

2. Methods

We accessed anonymous longitudinal clinical data (by 2014) of all HIV patients attending Integrated Treatment Centre, the largest HIV specialist clinic serving over half of the HIV caseload in Hong Kong. HIV patients are followed-up at 3 to 4 months' interval in accordance with protocol (http://www.hivmanual.hk/) modeled on international guidelines. Patients aged 18 or older at diagnosis were included in this study. Data retrieved included CD4, CD8, CD4/CD8 ratio, and viral load measurements at each follow-up time point, baseline sociodemographics (including sex, ethnicity, route of transmission), condition at diagnosis (age, HIV subtype, Cytomegalovirus [CMV] serology) and pre-treatment (age, interval from diagnosis to treatment initiation), regimen prescribed with records of start and end date, and AIDS

diagnosis. With reference to our previous studies, we classified patients by 3 age categories: 18–49 (young adults), 50–64 (middle-aged),[9] and ≥65 (elderly) years old. Using simple logistic regression models, we compared the characteristics between young adults and middle-aged, and between middle-aged and elderly.

In Hong Kong, a CD4 guided approach to treatment initiation was in place during the period when cohort subjects were diagnosed and therefore included in this study. To examine factors associated with late treatment initiation, we performed univariate analysis. With reference to previous study,[8] we defined late treatment initiation as patients with very low pre-treatment CD4 count (≤100cells/μL) or AIDS diagnosis before treatment initiation. We used CD4 level ≤100/μL instead of < 200/μL as the cut-off since 74% of our patients were Chinese, whose CD4 level was generally lower than the White in the general population (median of 670/μL for Chinese, median of 870/μL for German), as shown in other studies.[10–12] Patients who were not initiated on treatment or without pre-treatment CD4 level were excluded.

To study immune recovery after HAART initiation, we selected patients who were Chinese, treatment naïve, had been on treatment for ≥4 years, and had ever achieved viral load suppression (≤500 copies/mL) within 4 years of treatment for further analysis. We examined their CD4, CD8 and CD4/CD8 ratio over time to evaluate their immune recovery, and analyzed them separately as outcomes in multivariable linear generalized estimating equations (GEE) with unstructured working correlation matrix. Measurements between month -2 and month 60 were included. Variables including time (months from treatment initiation), age category, gender, late HIV diagnosis (i.e., AIDS diagnosis within 3 months from HIV diagnosis), late treatment initiation (yes vs no), baseline CMV serology (positive vs. negative), regimen (2 nucleoside reverse-transcriptase inhibitors plus a third compound: either a nonnucleoside reverse-transcriptase inhibitor [NNRTI] or antiretroviral other than NNRTI) and months from diagnosis to treatment initiation were examined in the model. To examine the interactions between time, age category, and late treatment initiation, we have added and dropped all combinations of these 3 variables with other variables in GEE models. Final GEE model for each immune marker was selected by the inclusion of significant predictors by manual stepwise backward approach. All statistical analyses were performed in IBM SPSS Statistics 21. P value <.05 was considered statistically significant. Complete case analyses were performed.

We obtained data access approval from the Department of Health, Hong Kong Special Administrative Region Government in compliance with the Personal Data (Privacy) Ordinance. Ethical approval was obtained from the Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee (CREC). Individual consent for this study was waived.

3. Results

As of the end of 2014, 3702 HIV patients have visited the clinic for clinical consultation. At diagnosis, 3674 patients were aged 18 or older (median age = 35, interquartile range (IQR) = 28–43). (Supplemental Digital Content 1, http://links.lww.com/MD/B791) By data collection end point, 75% (2754/3674) have initiated treatment, whereas 26% (832/3205) of the young adults, 19% (66/352) of the middle-aged, and 19% (22/117) of

Table 1

Characteristics of HIV patients at treatment initiation (n=2754).

	Age at treatment initiation (frequency/% or median/IQR)			(B) vs. (A) Crude odds ratio (95% CI)	(B) vs. (C) Crude odds ratio (95% CI)
	(A) Young adults—age 18–49 (n=2317)	(B) Middle-aged—age 50–64 (n=329)	(C) Elderly—age ≥65 (n=108)		
Male sex	1964 (85%)	288 (88%)	100 (93%)	1.26 (0.89 to 1.78)	0.56 (0.25 to 1.24)
Median age at diagnosis (IQR)	33.6 (27.7–39.7)	54.0 (50.8–58.2)	69.1 (65.7–72.0)	N/A	N/A
Ethnicity					
Chinese	1796 (78%)	287 (87%)	104 (96%)	1.98 (1.41–2.78)*	0.26 (0.09–0.75)*
Asian	338 (15%)	16 (5%)	2 (2%)	0.30 (0.18–0.50)*	2.71 (0.61–11.98)
White	127 (5%)	24 (7%)	2 (2%)	1.36 (0.86–2.13)	4.17 (0.97–17.95)
Others	56 (2%)	2 (1%)	0 (0%)	0.25 (0.06–1.02)	N/A
Mode of transmission	(n=2301)	(n=325)	(n=104)		
Heterosexual	885 (38%)	207 (64%)	80 (77%)	2.81 (2.21–3.57)*	0.53 (0.32–0.88)*
MSM	1264 (55%)	107 (33%)	23 (22%)	0.40 (0.32–0.51)*	1.73 (1.03–2.90)*
IDU	133 (6%)	8 (2%)	0 (0%)	0.41 (0.20–0.85)*	N/A
Others	19 (1%)	3 (1%)	1 (1%)	1.12 (0.33–3.80)	0.96 (0.10–9.33)
Positive CMV serology	(n=2312)	(n=328)	(n=107)		
	2117 (92%)	302 (92%)	101 (94%)	1.07 (0.70–1.64)	0.69 (0.28–1.72)
CD4 at diagnosis (cells/μL)	(n=2311)	(n=328)	(n=107)		
≤100	553 (24%)	114 (35%)	40 (37%)	Ref	Ref
101–200	268 (12%)	53 (16%)	16 (15%)	0.96 (0.67–1.37)	1.16 (0.60–2.26)
201–350	639 (28%)	75 (23%)	30 (28%)	0.57 (0.42–0.78)*	0.88 (0.50–1.53)
351–500	454 (20%)	45 (14%)	11 (10%)	0.48 (0.33–0.69)*	1.44 (0.68–3.04)
>500	397 (17%)	41 (13%)	10 (9%)	0.50 (0.34–0.73)*	1.44 (0.66–3.14)
Late HIV diagnosis[†]	365 (16%)	94 (29%)	44 (41%)	2.14 (1.64–2.79)*	0.58 (0.37–0.91)*
Median months from diagnosis to treatment initiation (IQR)	7.46 (2.10–33.02)	4.73 (2.14–20.98)	4.58 (1.81–15.99)	0.997 (0.99–1.001)	1.001 (0.995–1.01)
>6 mo	1230 (53%)	150 (46%)	45 (42%)	0.74 (0.59–0.93)*	1.17 (0.76–1.82)
CD4 at treatment initiation (cells/μL)	(n=2131)	(n=308)	(n=101)		
≤100	646 (30%)	116 (38%)	37 (37%)	Ref	Ref
101–200	458 (21%)	76 (25%)	28 (28%)	0.92 (0.68–1.26)	0.87 (0.49–1.53)
201–350	603 (28%)	69 (22%)	25 (25%)	0.64 (0.46–0.88)*	0.88 (0.49–1.59)
351–500	273 (13%)	30 (10%)	6 (6%)	0.61 (0.40–0.94)*	1.59 (0.62–4.13)
>500	151 (7%)	17 (6%)	5 (5%)	0.63 (0.37–1.07)	1.08 (0.37–3.14)
AIDS before treatment initiation	468 (20%)	108 (33%)	47 (44%)	1.93 (1.50–2.48)*	0.63 (0.41–0.99)*
Late treatment initiation[‡]	(n=2174)	(n=314)	(n=103)		
	785 (36%)	151 (48%)	54 (52%)	1.64 (1.29–2.08)*	0.84 (0.54–1.31)
Median year of treatment initiation (IQR)	2009 (2005–2012)	2009 (2006–2012)	2009 (2005–2012)	1.002 (0.98–1.02)	0.98 (0.93–1.03)

CI=confidence interval, CMV=cytomegalovirus, IDU=injection drug use, IQR=interquartile range, OR=odds ratio.

* $P<.05$.

[†] AIDS diagnosis within 3 months from HIV diagnosis.

[‡] Late treatment initiation—pre-treatment CD4 level (≤100 cells/μL) or AIDS diagnosis before treatment initiation.

the elderly (defining by age at diagnosis) have not yet been started on treatment. We analyzed 2754 patients on treatment (19190 persons-years follow-up) in this study. Among them, 2187 (79%) were Chinese, some 43% (928/ 2154) were infected with subtype CRF_01AE and 40% (867/2154) subtype B, whereas 31% (799/ 2540) and 38% (990/2591) had pretreatment CD4 ≤100 cells/μL and had late treatment initiation, respectively. The median number of months from diagnosis to treatment initiation was 6.82 (interquartile range [IQR]=2.10–31.23), and the median treatment duration was 62.19 months (IQR=28.93–111.79).

3.1. Pretreatment status by age category

Among patients who had ever been on HAART, we compared their baseline characteristics by age category. At treatment initiation, 2317 (84%) were young adults, 329 (12%) were middle-aged, whereas 108 (4%) were elderly. The middle-aged were significantly different from young adults in that they were composed of a higher proportion of heterosexually acquired infections and ethnic Chinese. They were more likely to have

lower CD4 levels at diagnosis and at treatment initiation, and presented with AIDS before treatment initiation. (Table 1) More were in late treatment initiation but less likely to have >6 months' interval from diagnosis to treatment initiation. However, there was no significant difference between middle-aged and elderly, except that the former were less likely to be in late diagnosis, were heterosexuals, and had AIDS before treatment initiation.

3.2. Factors associated with late treatment initiation in Chinese patients

Among 2754 patients, 2070 were Chinese and had pre-treatment CD4 count for defining late treatment initiation and otherwise. A total of 772 of 2070 (37%) Chinese patients were classified as having been late in treatment initiation. Middle-aged and elderly at diagnosis (crude odds ratio, odds ratio [OR]=1.88, 95% confidence interval [CI]=1.44–2.46 for middle-aged; OR=2.48, 95% CI=1.62–3.81 for elderly) and at treatment initiation (OR=1.85, 95% CI=1.43–2.39 for middle-aged; OR=2.15, 95% CI=1.43–3.22 for elderly), heterosexually acquired

Table 2

Comparison between Chinese patients with and without late treatment initiation (n = 2070).

	Not late (n = 1298)		Late* (n = 772)		Crude odds ratio (OR)	
	freq.	%	freq.	%	OR	95% CI
Male sex	1159	89%	692	90%	1.04	0.78–1.39
Median age at diagnosis (IQR)	34.86	28.15–42.78	39.89	31.89–48.69	1.03	1.03–1.04[†]
Young adults (18–49 y)	1135	87%	598	77%	Ref	
Middle-aged (50–64 y)	124	10%	123	16%	1.88	1.44–2.46[†]
Elderly (≥65 y)	39	3%	51	7%	2.48	1.62–3.81[†]
Mode of transmission	(n = 1291)		(n = 763)			
MSM	847	66%	293	38%	0.33	0.27–0.39[†]
Heterosexual	400	31%	441	58%	3.05	2.53–3.67[†]
Injection drug use	35	3%	21	3%	1.02	0.59–1.76
Others	9	1%	8	1%	1.51	0.58–3.93
Cytomegalovirus (CMV)	(n = 1298)		(n = 771)			
	1191	92%	711	92%	1.06	0.77–1.48
CD4 at diagnosis (cells/µL)						
≤100	17	1%	533	69%	Ref	
101–200	153	12%	87	11%	0.02	0.01–0.03[†]
201–350	511	39%	61	8%	0.004	0.002–0.01[†]
351–500	355	27%	44	6%	0.004	0.002–0.01[†]
>500	262	20%	46	6%	0.01	0.003–0.01[†]
Median months from diagnosis to treatment initiation (IQR)	11.2	3.02–34.53	2.99	1.58–10.41	0.99	0.99–0.99[†]
>6 mo	790	61%	244	32%	0.30	0.25–0.36[†]
Median year of treatment initiation (IQR)	2011	2007–2013	2007	2002–2010	0.90	0.88–0.91[†]
≥2012	546	42%	134	17%	0.29	0.23–0.36[†]
Median age at treatment initiation (IQR)	37.02	30.19–44.94	41	34.35–49.79	1.03	1.02–1.04[†]
Young adults (18–49 y)	1111	86%	583	76%	Ref	
Middle-aged (50–64 y)	140	11%	136	18%	1.85	1.43–2.39[†]
Elderly (≥65 y)	47	4%	53	7%	2.15	1.43–3.22[†]

* Patients with pretreatment CD4 level (≤100 cells/µL) or AIDS diagnosis before treatment initiation.

[†] $P < .05$.

infections (OR = 3.05, 95% CI = 2.53–3.67) or injection drug use (OR = 1.02, 95% CI = 0.59–1.76) were associated with late treatment initiation (Table 2). From 2012 onwards (OR = 0.29, 95% CI = 0.23–0.36), fewer patients were in late treatment initiation. Overall, patients with a long interval from diagnosis to treatment initiation (OR = 0.99, 95% CI = 0.99–0.99) were less likely to be late for treatment initiation. Among patients with late initiation, however, 68% of them had started treatment within 6 months from HIV diagnosis.

3.3. Immune recovery following HAART in Chinese patients

The impacts of age and late treatment initiation on immune recovery were examined in GEE models. A total of 913 Chinese patients who had been on treatment for ≥4 years were included in this part of the study. A total of 14,502 CD4 measurements, 14,490 CD8 measurements, and 14,490 CD4/CD8 ratio measurements from month 2 to month 60 were included in the analysis. Among them, 736 (80.6%) were young adults, 133 (14.6%) were middle-aged, and 44 (4.8%) were elderly. The median treatment duration was 101.5 months (IQR = 74.26–139.47 months). The level of CD4, CD8, and CD4/CD8 ratio across time from HAART initiation varied between age categories (Fig. 1A-C). With 3 immune markers as outcome, 3 sets of GEE models, A, B, and C were constructed (Table 3 and Supplemental Digital Content 2, http://links.lww.com/MD/B791).

The monthly rate of CD4 recovery after treatment initiation was 4.96 cells/µL in model A1 (Supplemental Digital Content 2, http://links.lww.com/MD/B791). Adding age as a variable and its

interaction with time in model A2, the monthly CD4 recovery rate was 5.26 cells/µL for young adults, 3.95 cells/µL for middle-aged and 3.36 cells/µL for elderly. Patients not on NNRTI regimen, in late diagnosis, with late treatment initiation, and shorter interval from diagnosis to treatment initiation had lower baseline CD4 level than their counterparts (Supplemental Digital Content 2, http://links.lww.com/MD/B791 models A5-A8). However, monthly CD4 recovery was faster over time among patients in regimen with antiretroviral other than NNRTI, in late treatment initiation and longer interval from diagnosis to treatment initiation. In the final GEE model for CD4 recovery (model CD4 in Table 3), patients with late treatment initiation had much lower baseline CD4 level than their counterparts, whereas patients in late HIV diagnosis had higher baseline CD4 level than those not in late HIV diagnosis, after adjusting other variables in the same model. In addition, although CD4 recovery rate among the late treatment initiation group varied significantly by age category, the recovery rate in non-late initiation patients was similar. CD4 recovery among elderly with late treatment initiation was 3.24 cells/µL/month, among middle-aged was 4.18 cells/µL/month, whereas among young adults was 5.7 cells/µL/month.

Different from CD4 recovery, decline of CD8 count is considered a desirable outcome. In Chinese patients on HAART, their CD8 declined at a rate of 0.89 cells/µL/month since treatment initiation. Age category was a significant predictor of CD8 change across time, with −0.50 cells/µL/month in young adults, −1.76 cells/µL/month in middle-aged and −4.34 cells/µL/month in elderly (Supplemental Digital Content 2, http://links.lww.com/MD/B791 model B2). It is noted that baseline CD8 for
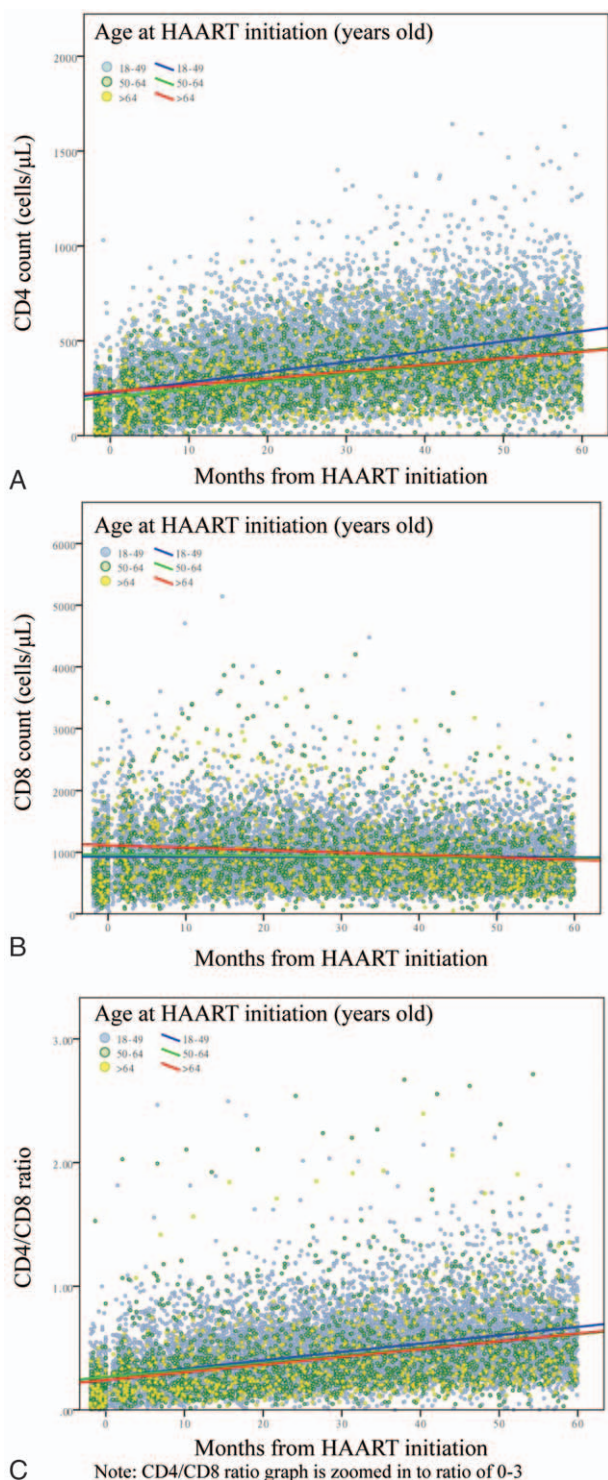
Figure 1. Scattered plots of (A) CD4 count, (B) CD8 count, and (C) CD4/CD8 ratio over time (months from highly active antiretroviral therapy initiation) with linear regression lines, stratified by age categories (18–49 years old, 50–64 years old, ≥65 years old).

elderly was much higher (Beta = 206.52, 95% CI = 64.07–348.97) than young adults. Patients who were male, positive baseline CMV positivity and regimen with antiretroviral other than NNRTI were associated with higher baseline CD8 level (model B3-B5). Also, patients with late treatment initiation had lower baseline CD8 level but slower monthly CD8 decline (model

B7). In the final model, in spite of a higher CD8 intercept, the decline of CD8 in elderly (−5.76 cells/μL/month) and middle-aged was faster (−2.91 cells/μL/month) than young adults (−1.24 cells/μL/month) (Table 3, model CD8). In the same model, baseline CD8 was lower in patients on NNRTI (Beta = −70.61, 95% CI = −104.93 to −36.28), but higher among male (Beta = 115.27, 95% CI = 68.2–162.33) and those whose baseline CMV serology was positive (Beta = 143.33, 95% CI = 73.39–213.27).

Using CD4/CD8 ratio as the marker of immune recovery, the monthly change of the ratio was 0.01 from treatment initiation in model C1 (Supplemental Digital Content 2, http://links.lww.com/MD/B791). The baseline CD4/CD8 among middle-aged (Beta = −0.03, 95% CI = −0.05 to −0.002) and elderly (Beta = −0.05, 95% C.I. = −0.08 to −0.02) was lower than the young adults (model C2). Comparing with young adults, middle-aged had slower CD4/CD8 ratio recovery rate, whereas elderly had similar rate. Patients with positive baseline CMV serology had lower ratio at baseline (model C4). Male and patients on NNRTI-based regimen had slower CD4/CD8 ratio increase over time than their counterparts (model C3, C5). Also, CD4/CD8 ratio recovery of patients in late diagnosis, with late treatment initiation and who had a long interval from diagnosis to treatment initiation, was faster, even though the baseline of those in late diagnosis and late treatment initiation was lower (model C6–8). In the final model (Table 3, model CD4/CD8), though patients with late treatment initiation had lower baseline CD4/CD8 ratio, their recovery rate was faster (interaction with time: Beta = 0.001, 95% CI = 0.0002–0.001), holding late HIV diagnosis, male sex, and baseline CMV constant. Age was not a significant predictor in the final model of CD4/CD8 ratio and was excluded.

4. Discussion

Our study findings highlighted the association of age category at treatment initiation with the pattern and pace of immune recovery of HIV patients after HAART. This is an important perspective in HIV treatment now that more patients are entering older age. In our cohort, the immune recovery of middle-aged adult Chinese was significantly slower than young adults, but their CD4 recovery was faster than the elderly. Of note, our findings identified slower CD8 decline in the middle-aged compared to elderly, making middle-aged the age category with the slowest recovery of CD4/CD8 ratio. Besides age, we also identified late diagnosis and late treatment initiation as the predictors of CD4 recovery, whereas NNRTI, male sex, and baseline CMV as the predictors of CD8 decline. All of these were predictors of CD4/CD8 ratio recovery. While elderly people are long known to be performing less favorably in immune recovery, our results reminded us of the unique challenges faced by the middle-aged.

While late diagnosis and treatment initiation were significant predictors of CD4 and CD4/CD8 ratio recovery, they were significantly associated with age category. Both middle-aged and elderly were more likely to be in late HIV diagnosis and treatment initiation, an observation consistent with other studies.[6,8] Elderly people had lower perceived risk of HIV infection and were more likely to ignore the symptomatology of HIV/AIDS, which may appear to be similar with other common chronic illnesses.[6] With delayed HIV diagnosis, they were therefore more likely to be late for treatment initiation, as shown by the low CD4 level at diagnosis in Tables 1 and 2.

In addition to the well-known impact of age on CD4 recovery as reported in studies locally and internationally,[1,3,4] we

Table 3

Factors associated with post-treatment CD4 count, CD8 count, and CD4/CD8 ratio in multivariable generalized estimating equations.

Variables	Model CD4		Model CD8		Model CD4/CD8 ratio	
	Beta	95% Wald	Beta	95% Wald	Beta	95% Wald
Time	4.77	4.49 to 5.06[*]	−1.24	−1.66 to −0.81[*]	0.01	0.01 to 0.01[*]
Age at treatment initiation						
elderly (age ≥65 y) (ref: young adults)	−1.86	−28.81 to 25.09	203.13	42.75 to 363.51[*]	/	
middle-aged (age 50–64 y) (ref: young adults)	−14.54	−28.21 to −0.87[*]	57.44	−27.72 to 142.6	/	
elderly × time (ref: young adults × time)	/		−4.52	−6.79 to −2.24[*]	/	
middle-aged × time (ref: young adults × time)	/		−1.67	−3.01 to −0.34[*]	/	
late Tx (ref: not in late Tx)	−167.58	−180.07 to −155.09[*]	/		−0.21	−0.23 to −0.19[*]
late Tx × time (ref: not in late Tx × time)	/		/		0.001	0.0002 to 0.001[*]
Interaction between age, late Tx and time (ref: young adults × not in late Tx × time)						
elderly × late Tx × time	−1.53	−2.52 to −0.54[*]	/		/	
elderly × not late Tx × time	−1.3	−2.37 to −0.22[*]	/		/	
middle-aged × late Tx × time	−0.59	−1.17 to −0.01[*]	/		/	
middle-aged × not late Tx × time	−1.16	−1.78 to −0.53[*]	/		/	
young adults × late Tx × time	0.93	0.51 to 1.34[*]	/		/	
Other variables						
Late Dx (ref: not in late Dx)	31.22	13.9 to 48.53[*]	/		0.04	0.02 to 0.06[*]
NNRTI-based regimen (ref: regimen other than NNRTI)	/		−70.61	−104.93 to −36.28[*]	/	
Male sex (ref: female)	/		115.27	68.2 to 162.33[*]	−0.09	−0.12 to −0.06[*]
Positive baseline CMV (ref: negative CMV)	/		143.33	73.39 to 213.27[*]	−0.09	−0.13 to −0.06[*]

Beta = linear regression coefficient, CMV = cytomegalovirus, Dx = diagnosis, late Dx = AIDS diagnosis within 3 months from HIV diagnosis, late Tx = pre-treatment CD4 level (≤100 cells/μL) or AIDS diagnosis before treatment initiation, NNRTI = non-nucleoside reverse-transcriptase inhibitors, Time = months from treatment initiation, Tx = treatment.

[*] $P < .05$.

observed that these responses varied between late and non-late treatment initiation. Middle-aged adults in late treatment initiation had faster CD4 recovery than elderly. However, the difference of the 2 age categories in non-late treatment initiation was not obvious. Though age at treatment initiation was a known significant predictor for CD4 recovery,[7] aging during treatment (the duration on treatment and increasing age during treatment) was not associated with CD4 decline in the first 5 years of treatment.[13] These results suggested that, compared to aging during treatment, pretreatment age might have bigger impact on CD4 recovery after treatment initiation. The variation of immune recovery rate by pretreatment age category and/or late treatment initiation observed in our study lends support to this phenomenon. Although the interval from HIV infection to treatment initiation might affect the age at which treatment begins, the implications for late HIV diagnosis and treatment initiation would need to be addressed separately. Late diagnosis demands effective public health intervention such as testing scaling up, whereas late treatment initiation could be addressed by developing appropriate health service strategy .[14,15] A study has concluded that older patients would have higher benefits under early treatment initiation strategy,[16] even though their definition of elderly differed from ours.

Although most studies had used CD4 as a marker for immune recovery, CD8 and CD4/CD8 ratio should not be ignored in view of their association with chronic inflammation and immune activation.[17–19] Expressing the pace of immune recovery by CD4/CD8 ratio, the rate of change after treatment initiation in middle-aged patients in our study was slowest compared to other age categories. Our results on CD4/CD8 ratio change were slightly different from another study.[20] In the latter study, older patients were more likely to have inverted CD4/CD8 ratio (<0.9) and less likely to have CD4/CD8 normalization. Continuous age variable was used instead of classifying middle-aged as one category, which might have smoothed the sudden drop of CD4/CD8 ratio recovery rate in middle-aged over the whole age range.

However, we found that CMV was a significant predictor of CD8 and CD4/CD8 ratio, but not CD4. Even though we used baseline CMV serostatus as predictor, our finding was consistent with another study examining the association of CMV serostatus with CD8 and CD4/CD8 ratio.[21,22]

Our study carries some limitations. First, in the absence of a universal standard for "middle-age," we acknowledge that defining it as 50–64 years-old might be arbitrary even though our approach has taken reference from other related studies.[9,17] We performed sensitivity analyses (results not shown) to assess the impact of varying this definition for age category. The variables significantly associated with age categories were similar when the definition was changed in sensitivity analysis, except CMV serostatus, which became different if patients aged 40 to 45 years were grouped as middle-aged. Second, because of small sample size of non-Chinese patients and high variation of CD4 level by ethnicity in general population,[10,12] the temporal change of immune recovery markers were examined among Chinese patients only. Although such an approach carried an advantage of minimizing the impact of ethnic heterogeneity of the studied population, the results could theoretically be applicable to Chinese HIV patients only, and caution must be exercised when extrapolating results to other ethnicities. Third, we are also mindful of the cautious use of nevirapine (NVP), when NNRTI-based regimens were considered for women and those with high CD4 count.[23,24] We have performed another set of GEE models examining NNRTI as a factor with the exclusion of all time points with NVP (results not shown) but could not find any significant difference. Fourth, limited by data availability, the characterization of immune recovery was limited to markers of CD4, CD8, and CD4/CD8 ratio only.

Finally, with the generally higher mortality rate of elderly HIV patients compared to the young adults,[25] the former was often regarded as the group in urgent need of treatment. Our results showed that although a high proportion of elderly (age above 65) were in late HIV diagnosis, their current treatment initiation

status was in fact close to "immediate." On the contrary, the immune recovery of middle-aged in our cohort was far from satisfactory after treatment initiation. Whereas middle-aged adults were slightly faster than elderly in their rate of CD4 recovery, their CD4/CD8 ratio recovery was even slower. As middle-aged were less likely to be in late diagnosis than the elderly, we believe that they have not been initiated treatment as early as that for the elderly, especially in time of a CD4-guided approach to treatment initiation. The middle-aged patients would have a better immune response if they had been initiated treatment earlier, that is, when they were younger, or even at the age of young adults. *Treat All* is a new recommendation of WHO,[14] a strategy just started but not yet fully implemented in places like Hong Kong. As a proportion of patients diagnosed in early years might not have been initiated on treatment owing to various reasons, there is the need to focus on those with unmet need because of poorer anticipated outcome. Interventions for improving treatment uptake of middle-aged HIV patients should be prioritized to maximize the benefits of the strategy.

Acknowledgments

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