Immune recovery of middle-aged HIV patients following antiretroviral therapy
An observational cohort study
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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. 0.010/1/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.[1,4] 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.[1,3] 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. 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 transitioning 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, delayed HIV diagnosis, aging 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. 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. 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, 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), 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, we defined late treatment initiation as patients with very low pre-treatment CD4 count (<100 cells/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). 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 category, and late treatment initiation, we have added and dropped all combinations of these 3 variables with other variables in GEE models.

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
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
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 = 1298) (n = 772)

- MSM: 647 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)

- n = 972: Crude odds ratio (OR) and 95%CI
- Ref

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 0.002–0.02
- 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)

- >6 mo: 700 61% 244 32% 0.30 0.25–0.36

Median year of treatment initiation (IQR)

- ≥2012: 546 42% 134 17% 0.29 0.23–0.36

Median age at treatment initiation (IQR)

- ≥2012: 37.02 30.19–44.94 41 34.35–49.79 1.03 1.02–1.04

Young adults (18–49 y) 140 11% 136 18% 1.85 1.43–2.39
Elderly (≥65 y) 47 4% 53 7% 2.15 1.43–3.22

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 101.3 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
elderly was much higher (β = 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 (−3.76 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 (β = −70.61, 95% CI = −104.93 to −36.28), but higher among male (β = 115.27, 95% CI = 68.2–162.33) and those whose baseline CMV serology was positive (β = 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/MDB791). The baseline CD4/CD8 among middle-aged (β = −0.03, 95% CI = −0.05 to −0.002) and elderly (β = −0.05, 95% CI = −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: β = 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. 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. 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, we
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, aging during treatment (the duration on treatment and increasing age during treatment) was not associated with CD4 decline in the 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.

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, the results could theoretically be applicable to the 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.

Our study carries some limitations. First, in the absence of a universal standard for “middle-age,” 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, 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, when NNRTI-based regimens were considered for women and those with high CD4 count.
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 the age of young adults.

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