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Short Communication
Factors Influencing Time to CD4$^+$ T Cell Counts >200 Cells/mm^3 in HIV-Infected Individuals with CD4$^+$ T Cell <50 Cells/mm^3 at the Time of Starting Combination Antiretroviral Therapy

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Abstract

We evaluated factors influencing time to CD4$^+$ T cell counts >200 cells/mm^3 in HIV-infected individuals with CD4$^+$ T cell <50 cells/mm^3 starting combination antiretroviral therapy (cART). We included a total of 29 patients on successful cART for more than 1 year. In a logistic regression model, higher pre-cART CD4$^+$ T cell counts were significantly associated with shorter time to CD4$^+$ T cell counts >200cells/mm^3 in HIV-infected individuals with baseline CD4$^+$ T cell <50 cells/mm^3. In survival analysis, patients having higher pre-cART CD4$^+$ T cell counts, especially 40–49 cells/mm^3, were at significantly higher risk of achieving CD4$^+$ T cell counts >200 cells/mm^3.

Introduction

Survival in human immunodeficiency virus (HIV)-infected individuals has improved with the introduction of combination antiretroviral therapy (cART).[1,2] However, late diagnosis of HIV infection still contributes to poor medical outcomes and the continuation of viral transmission.[3–5]

Of the immunologic markers, the CD4$^+$ T cell levels are not only comprehensively used for initiating HIV therapy and prophylaxis for opportunistic infections,[6,7] but also are an important criterion for categorizing HIV-related clinical conditions.[8,9] HIV-infected patients with CD4$^+$ T cell counts <200 cells/mm^3 are at risk for developing *Pneumocystis* infections.[7] In particular, CD4$^+$ T cell counts <50 cells/mm^3 are predisposing factors for all opportunistic infections (OIs) including *Mycobacterium avium* complex (MAC) and cytomegalovirus (CMV) infections.[7] Thus, in HIV-infected individuals, to prevent opportunistic infections it is important that CD4$^+$ T cell counts are increased to >200 cells/mm^3 as soon as possible.

However, to our knowledge, little is known about factors influencing time to CD4$^+$ T cell counts >200 cells/mm^3 in HIV-infected individuals with baseline CD4$^+$ T cell counts <50 cells/mm^3 at the start of cART.

Materials and Methods

A retrospective case-control study was conducted at an urban hospital in Seoul, South Korea. HIV-1-infected persons, who started cART between 1996 and 2010, were aged 18 years or older at treatment initiation, had CD4$^+$ T cell counts <50 cells/mm^3 at the time of starting cART, and had sustained virological suppression (HIV RNA <400 copies/ml) over 1 year of cART were eligible for this study. Patients who had any treatment interruption for more than 1 month were excluded. CD4$^+$ T cell counts of each individual were evaluated every 3 months (within a window of ±1 month). The pre-cART CD4$^+$ T cell counts were mostly measured when the treatment was started.

During this study, 593 HIV-infected patients were retrospectively analyzed. Among these patients, death and follow-up loss were 31 and 265, respectively. Also, the study included nine treatment-naive patients. The study included 288 patients who started cART as well, and 75 of these 288 patients had interruptions of treatment or virological failures. Among 222 patients who had maintained a suppressed viral load over 1 year after initiating cART were 29 HIV-infected patients who had CD4$^+$ T cell counts <50 cells/mm^3 at the time of starting cART. All enrolled patients were initially treated with cART at CD4$^+$ T cell counts <50 cells/mm^3 due to late diagnosis of HIV infection.

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The following variables were assessed: age at therapy initiation (years); gender; reported route of infection; prior acquired immunodeficiency syndrome (AIDS) diagnosis at cART initiation; hepatitis B or C coinfection; tuberculosis (TB) coinfection during the follow-up; antiretroviral therapy (ART) regimens [two nucleoside analog reverse transcriptase inhibitors (NRTIs) + nonnucleoside reverse transcriptase inhibitor (NNRTI), two NRTIs + protease inhibitor (PI), or other combination] at cART initiation; $CD4^+$ T cell count (cells/mm^3), $CD8^+$ T cell count (cells/mm^3), and HIV viral load (copies/ml) at cART initiation. The Centers for Disease Control and Prevention (CDC) classification was determined for each individual.[10] The most severe CDC category recorded was listed as the clinical status.

We estimated duration (months) from the initiation of cART to the date of test reporting $CD4^+$ T cell counts >200 cells/mm^3 in each individual. Patients were then categorized into two groups depending on the median time to increase from $CD4^+$ T cell counts <50 cells/mm^3 to >200 cells/mm^3 after starting cART. One group was deemed the slow increase group as its interval times were more than the median time and the other group was deemed the fast increase group as its interval times were faster than the median time. Pre-cART $CD4^+$ T cell counts were mostly measured when cART was started. Even though pre-cART $CD4^+$ T cell counts were measured within 2 weeks before initiating cART in eight patients, there were four cases of the slow increase group and four cases of the fast increase group.

To evaluate predictors of slow increase, we performed logistic regression analyses. Variables with a p-value of <0.1 in the univariate analysis were included for the multivariate analysis. We also evaluated outcomes of $CD4^+$ T cell count >200 cells/mm^3 following cART initiation using a survival analysis method. The survivor function for $CD4^+$ T cell count >200 cells/mm^3 was compared using Cox proportional hazard models. Time was calculated from the initiation of cART and ended at the time of reporting $CD4^+$ T cell counts >200 cells/mm^3. The final multivariate model included all covariates that remained significant at the 0.10 level (two sided). The analyses were performed using SPSS (version 18).

Results

A total of 29 patients who fulfilled the inclusion criteria were identified. The median age was 50 (range, 35–75) years, and 96.6% (28/29) of the subjects were male. The most common exposure category was men having sex with men (MSM) (44.8%), followed by heterosexual contact (10.4%). These 29 patients had achieved an absolute level of CD4 counts of 200 cells/mm^3 and had a median interval time of 12 (range, 3–42) months up to >200 cells/mm^3 of $CD4^+$ T cell counts after cART. Slow (n=15) and fast (n=14) increase groups had median interval times of 18.3 and 3.5 months, respectively.

The demographic and clinical characteristics of each group are shown in Table 1. Compared with patients who exhibited a fast increase in $CD4^+$ T cell counts, patients who showed a slow increase had significantly lower pre-cART $CD4^+$ T cell counts. Only the slow increase group had TB coinfections. In the multivariate analysis, lower pre-cART $CD4^+$ T cell count was significantly associated with the slow increase of $CD4^+$ T cell counts >200 cells/mm^3 (odds ratio 0.873; 95% confidence interval 0.781–0.975; p=0.016) (Table 2).

We also evaluated the factors associated with the time to the increase of $CD4^+$ T cell counts >200 cells/mm^3 since cART initiation in Cox proportional hazard analysis. In the multivariate model, patients having a higher pre-cART $CD4^+$ T cell count, especially those whose baseline count was greater than 40 cells/mm^3, had a significantly higher rate of $CD4^+$ T cell counts >200 cells/mm^3 (adjusted hazard ratio 6.633; 95% confidence interval 1.121–39.230; p=0.037) (Table 3).

Table 1. The Demographic and Clinical Characteristics of HIV-Infected Individuals with $CD4^+$ T Cell <50 Cells/mm^3 at the Start of Combination Antiretroviral Therapy

Variables	*Slow increase group* N=*15*, n *(%)*	*Fast increase group* N=*14*, n *(%)*	*Total* N=*29*, n *(%)*	p-*value*
Male gender	14 (93.3)	14 (100)	28 (96.6)	1.000
Age at starting cART, median, years (range)	47 (35–79)	51 (35–75)	50 (35–75)	0.323
Mode of transmission				
Homosexual contacts	8 (53.3)	5 (35.7)	13 (44.8)	0.462
Heterosexual contacts	2 (13.3)	1 (7.1)	3 (10.4)	1.000
Unknown and others[a]	5 (33.3)	8 (57.1)	13 (44.8)	
Pre-cART $CD4^+$ T cell count, median (IQR), cells/mm^3	14 (6–18)	28 (6–47)	17 (10–29)	0.032
Pre-cART VL, median (IQR), $\log_{10}$ copies/ml	5.36 (4.72–5.69)	5.31 (3.88–6.30)	5.34 (4.82–5.34)	0.921
Pre-cART $CD8^+$ T cell count, median (IQR), cells/mm^3	370 (197–456)	493 (279–748)	413 (222–664)	0.076
Initial cART regimen				
PI plus 2 NRTIs	7 (46.7)	6 (42.9)	16 (55.2)	0.837
NNRTI plus 2 NRTIs	8 (53.3)	8 (57.1)	13 (44.8)	0.837
TB coinfection at starting cART	3 (20.0)	0 (0.0)	3 (10.3)	0.224
HBV coinfection at starting cART	0 (0.0)	2 (14.3)	2 (6.9)	0.224
CDC stage at starting cART				
B3	3 (20.0)	1 (7.1)	4 (13.8)	0.598
C3	12 (80.0)	13 (92.9)	25 (86.2)	0.598

[a]Unknown and others: 12 unknown and 1 blood product.

HIV, human immunodeficiency virus; cART, combination antiretroviral therapy; IQR, interquartile range; VL, viral load; PI, protease inhibitor; NRTI, nucleoside analog reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; TB, tuberculosis; HBV, hepatitis B virus; CDC, Centers for Disease Control and Prevention.

Table 2. Multivariate Analysis of Time to $CD4^+$ T Cell Counts >200 Cells/mm^3 After Combination Antiretroviral Therapy in HIV-Infected Individuals with Baseline $CD4^+$ T Cell <50 Cells/mm^3

Variables	*Slow increase group N=15*	*Fast increase group N=14*	*Odds ratio (95% CIs)*	p-*value*
Age at starting cART (per 1 year increase), median, years (range)	47 (35–79)	51 (35–75)	1.045 (0.948–1.152)	0.375
Pre-cART $CD8^+$ T cell counts (per 100 cells/mm^3 increase), median (IQR), cells/mm^3	14 (6–18)	28 (6–47)	0.888 (0.657–1.201)	0.442
Pre-cART $CD4^+$ T cell counts (per 1 cell/mm^3 increase), median (IQR), cells/mm^3	370 (197–456)	493 (279–748)	0.873 (0.781–0.975)	0.016

cART, combination antiretroviral therapy; IQR, interquartile range; HIV, human immunodeficiency virus; CIs, confidence intervals.

Discussion

The $CD4^+$ T cell count is an important determinant of disease stage and prognosis in HIV-infected individuals.[8,9] According to Lee *et al*., the proportion of individuals with a late diagnosis defined by a $CD4^+$ T cell count <200 cells/mm^3 at the time of diagnosis increased annually from 2000 to 2007 in South Korea.[11] Late diagnosis, especially $CD4^+$ T cell count <50 cells/mm^3 at the time of diagnosis, results in delayed treatment, increasing OIs, and an increased risk of transmission.[3–5] Thus, there is still a high risk of mortality in HIV-infected individuals due to late diagnosis.[3–5]

The factors that affect the extent of the increase of $CD4^+$ T cell counts in patients receiving cART have been studied. Some have reported that the baseline $CD4^+$ T cell count influences the rate of immune reconstitution,[12,13] whereas others have found no evidence of such an association.[14,15] However, to our knowledge, little is known about HIV-infected individuals with pre-cART $CD4^+$ T cells <50 cells/mm^3, which was a predisposing factor of all OIs including MAC and CMV infections. To the best of our knowledge, our study represents the first report regarding factors influencing time to reach $CD4^+$ T cell counts >200 cells/mm^3 in HIV-infected individuals with $CD4^+$ T cell counts <50 cells/mm^3 at the time of starting ART.

In this study, pre-cART $CD4^+$ T cell counts were significantly associated with time to $CD4^+$ T cell counts >200 cells/mm^3 in HIV-infected individuals with $CD4^+$ T cell counts <50 cells/mm^3 at the time of starting cART. In other words, the lower the pre-cART $CD4^+$ T cell counts among patients with $CD4^+$ T cell counts <50 cells/mm^3, the slower was the increase of $CD4^+$ T cell counts >200 cells/mm^3.

Also, we evaluated the impact of pre-cART $CD4^+$ T cell counts in patients with $CD4^+$ T cell counts <50 cells/mm^3 at the time of achieving a $CD4^+$ T cell count >200 cells/mm^3 using survival analyses. Compared to those who started with a CD4 of 0–10 cells/mm^3, a pre-cART $CD4^+$ T cell count of 40–49 cells/mm^3 showed a higher rate of achieving a $CD4^+$ T cell count >200 cells/mm^3. Moreover, pre-cART $CD4^+$ T cell counts of 30–39 cells/mm^3 showed a tendency to be greater in achieving $CD4^+$ T cell counts >200 cells/mm^3 (p-value = 0.057). Therefore, in late diagnoses, especially for $CD4^+$ T cell counts <40 cells/mm^3, we need to immediately consider cART and be more aware of OIs and viral transmission during cART. However, the results of this study are based on a small sample size, so if more samples are added, more precise statistical significance can be identified.

Also, in our study, TB was observed in three patients in only the slow increase group and none in the fast increase

Table 3. Cox Proportional Hazards Analysis of an Increase of $CD4^+$ T Cell count >200 Cells/mm^3 Following Combination Antiretroviral Therapy Initiation

Variables	*Median time to event (months)*	n *(%) of events (CD4 >200 cells/mm^3)*	*Unadjusted HR (95% CI)*	p-*value*	*Adjusted HR (95% CI)*	p-*value*
Age at starting cART, years						
≤50	10.5	15 (51.7)	1		1	
50>	9.7	14 (48.3)	0.897 (0.418–1.924)	0.78	0.874 (0.374–2.041)	0.756
Mode of transmission						
Homosexual contacts	10.9	13 (44.8)	1		—	—
Heterosexual contacts	11.7	3 (10.4)	1.362 (0.378–4.912)	0.637	—	—
Pre-cART $CD4^+$ T cell count, cells/mm^3						
<10	17.4	7 (24.1)	1		1	
10–19	11.7	12 (41.4)	1.001 (0.380–2.640)	0.998	0.990 (0.374–2.618)	0.983
20–29	8.3	3 (10.3)	2.404 (0.591–9.789)	0.221	2.234 (0.511–9.753)	0.285
30–39	9.7	5 (17.2)	3.594 (0.980–13.180)	0.054	3.538 (0.963–12.996)	0.057
40–49	2.7	2 (7.0)	6.25 (1.102–35.461)	0.039	6.633 (1.121–39.230)	0.037
Initial cART regimen						
PI plus 2 NRTIs	10.5	13 (44.8)	1		—	—
NNRTI plus 2 NRTIs	13.1	16 (55.2)	0.774 (0.365–1.638)	0.503	—	—

cART, combination antiretroviral therapy; HR, hazard ratio; CIs, confidence intervals; VL, viral load; IQR, interquartile range; PI, protease inhibitor; NRTI, nucleoside analog reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.

group. However, there was no significant association between TB and time to $CD4^+$ T cell counts >200 cells/mm^3, although several studies showed that TB influenced the increase of $CD4^+$ T cell counts during cART.[16,17]

Our study has several limitations. First, our results were not applicable to females with HIV infection. Gender is a very important epidemiological variable but in our data, women comprised only 3%, so we did not consider gender in our data analysis. This is due to the fact that HIV-infected women in Korea are rare (only about 9%) and our study did not have enough women.[18] Second, the sample size was small. However, we have enhanced the power by subdividing the group with smaller categories. A multicenter study is under progress for more concrete results. Third, as in all retrospective studies, there is a potential for bias and inaccurate data collection. Further prospective studies, with larger patient populations involving multiple centers, are necessary to ascertain the relevant influencing factors accurately. Fourth, although $CD4^+$ T cell counts of each individual were evaluated every 3 months in the two groups, the time to achieve a $CD4^+$ T cell count >200 cells/mm^3 is likely to be affected by interval censoring because of a window of ± 1 month. Lastly, we used a single $CD4^+$ T cell count for each time point, and "the regression to the mean" could bias our results.

In conclusion, the pre-cART $CD4^+$ T cell count was significantly associated with time to $CD4^+$ T cell counts >200 cells/mm^3 in HIV-infected individuals with $CD4^+$ T cell counts <50 cells/mm^3 at the start of cART. Therefore, in late diagnoses, especially for $CD4^+$ T cell counts <40 cells/mm^3, we need to immediately consider cART and be more aware of OIs and viral transmission during cART.

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Author Disclosure Statement

No competing financial interests exist.

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