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ORIGINAL ARTICLE

The influence of low-level viremia on CD4⁺ cell count in human immunodeficiency virus–infected patients

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Abstract

Background: Following initiation of combined antiretroviral therapy, the majority of human immunodeficiency virus–infected patients experience immune reconstitution indicated by virologic suppression and an increase in peripheral CD4⁺ T-cell counts. Some patients may suffer from low-level viremia, which was reported to be significantly associated with acquired immunodeficiency syndrome cases, virologic failure, and death. We aimed to further investigate the influence of low-level viremia on CD4⁺ T-cell count.

Methods: In our study, we included human immunodeficiency virus-seropositive patients on combined antiretroviral therapy, for at least 6 months, who received at least one assessment of human immunodeficiency virus plasma viral load and CD4⁺ cell count every 6 months, from January 2009 to January 2019. The copy-year viremia was determined by calculating the area under the curve of the plasma human immunodeficiency virus viral load.

Results: When comparing patients with a mean CD4⁺ cell count <200 cells/μL, there was no significant difference between patients with a mean viral load <1000 copies/mL and patients with a mean viral load ≥1000 copies/mL ($p = 0.219$). Among those with a mean viral load <1000 copies/mL, a higher proportion of patients had a mean CD4⁺ cell count ≥500 cells/μL ($p < 0.001$). The mean CD4⁺ cell count of patients with copy-years viremia ($\log_{10}$) <4 (577.7, interquartile range 429.2-736.7) was significantly higher than that of patients with copy-years viremia ($\log_{10}$) ≥4 (443.3, interquartile range 319.0-558.4) ($p < 0.001$). In multivariate logistic regression analysis, we observed that malignancy without history, lower copy-years viremia, and high nadir CD4⁺ cell count were independent predictors of mean CD4⁺ cell count ≥500 cells/μL.

Conclusion: Human immunodeficiency virus–infected patients with a history of malignancy, high copy-year viremia, and lower nadir CD4⁺ cell counts should be monitored carefully in clinical settings.

Keywords: CD4⁺ cell count; Human immunodeficiency virus; Low-level viremia

1. INTRODUCTION

Combined antiretroviral therapy (cART) effectively contributes to the suppression of human immunodeficiency virus (HIV) viremia and reduced the mortality rate of HIV-infected patients.[1] However, low-level viremia (LLV) is common in HIV-infected patients under cART with 20% to 40% intermittent and 4% to 27% persistent LLV.[2–6] LLV was reported to be significantly associated with acquired immunodeficiency syndrome (AIDS) events, virologic failure, and death.[7] Cole et al developed copy-years viremia (VCY) as a measure of cumulative HIV plasma viral load (VL), where the increase in VCY was associated with an increased hazard ratio of AIDS or death, independent of the infection duration, age, and race.[8] Thus far, the definition of virologic failure differs among international guidelines, including the Department of Health and Human Services (DHHS), the European AIDS Clinical Society, and the World Health Organization (WHO).[9–11] No consensus is achieved on the treatment strategy for LLV and its associated influence on human immunity.

CD4⁺ T cells are the main targets of HIV. Following cART initiation, the majority of HIV-infected patients experience virologic suppression and an increase in peripheral CD4⁺ T-cell counts, which is a hallmark of immune reconstitution. According to the international guidelines, the absolute CD4⁺ T-cell count threshold is required to determine the initiation of opportunistic infection prophylaxis. Additionally, a low CD4⁺/CD8⁺ ratio with increased immune activation increased morbidity and mortality in HIV-infected patients.[12,13]

According to Zhou et al, after cART initiation, CD4⁺ cell counts continued to increase with detectable concurrent HIV VL. However, to maintain a positive CD4⁺ cell count slope, HIV VL needs to be kept low.[14] We conducted this study to further investigate the influence of LLV on CD4⁺ cell count in HIV-infected patients, receiving cART.

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2. METHODS

2.1.Setting and study design

This retrospective longitudinal cohort study was conducted at a 2900-bed tertiary medical center, Taipei Veterans General Hospital, from January 2009 to January 2019. The patients enrolled were classified according to three different viremia statuses: viral-suppression group, those with HIV VL test results always <50 copies/mL; LLV group, including those with HIV VL test results ranging from 50 to 1000 copies/mL; virologic failure group, those with HIV VL test results always >1000 copies/mL, after 6 months of ART.[9] The HIV-seropositive patients on cART for at least 6 months were included in the study, who received at least one assessment of HIV plasma VL and CD4⁺ cell count every 6 months. Patients aged <20 years were excluded. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (approval no. 2012-07-003AY).

2.2. Variables and definitions

Clinicians reviewed the patient's medical records. Data on age, sex, body weight, underlying diseases, HIV plasma VL, serum CD4⁺ T-cell count, and cART were collected. Intermittent LLV (iLLV) was defined as HIV plasma VL levels between 50 and 999 copies/mL within 1 year, followed by another value below assay limits.[15] Persistent LLV (pLLV) was defined as HIV plasma VL level between 50 and 999 copies/mL in at least two determinations, above 1 year.[4] All undetectable HIV plasma VL (negative result <20) was set as the number "19" for consistency of the data. HIV VCY was determined by calculating the area under the curve for plasma HIV VL.[8] For all patients, VCY was calculated on the entire set of available HIV VL cases from January 2009 to January 2019. In Taiwan, HIV-positive patients are provided free-of-charge cART, which was introduced on 1 April 1997.[16] Laboratory data include HIV plasma VL, CD4⁺ cell count, serum creatinine level, and treponemal test plus rapid plasma reagin titers, calculated every 3 months in the first year of cART initiation and every 6 months thereafter for HIV VL <50 copies/mL. According to the national HIV treatment guidelines, serology of hepatitis viruses, including hepatitis B surface antigen and anti-hepatitis C antibody (anti-HCV), was determined at baseline annually, and when indicated clinically, such as when elevated aminotransferase levels were noted.

2.3. Statistical analysis

Chi-square or Fisher's exact tests were used to analyze categorical data. The Student's *t* test or Mann-Whitney *U* test was used to continuously assess the data. Two-tailed tests were used to determine statistical significance, and a value of $p < 0.05$ was considered significant. To identify the independent predictors of a mean CD4⁺ cell count ≥500 cells/μL, we used logistic regression analysis and adjusted for potential confounders. All statistical analyses were performed using SPSS software version 19 (SPSS Inc., Chicago, IL, USA).

3. RESULTS

A total of 431 individuals were included in the study from January 2009 to January 2019. Among our study population, 414 (96.1%) were male and the majority (388, 90.0%) transmitted the disease through men who had sex with men (MSM). Among the three groups, virologic suppression, LLV, and virologic failure, there were no significant differences in sex, body weight, or underlying comorbidities. Patients in the virologic failure group were the youngest (34.0 years, interquartile range [IQR] 28.0-41.0) and were diagnosed with more incidences of opportunistic infections (58, 31%, $p = 0.005$) (Table 1).

To evaluate the influence of serum HIV RNA levels on CD4⁺ cell counts, patients were classified as those with mean VL <1000 and ≥1000 copies/mL. The mean CD4⁺ cell count of patients with VL <1000 copies/mL was significantly higher than that of patients with VL ≥1000 copies/mL ($p < 0.001$). However, when comparing patients with a mean CD4⁺ cell count of <200 cells/μL, there was no significant difference between the two groups ($p = 0.219$). Among those with a mean VL ≥1000 copies/mL, a higher proportion of patients had a mean CD4⁺ cell count of <500 cells/μL ($p < 0.001$). Among participants with mean VL <1000 copies/mL, both the percentage of absolute CD4⁺ cell count and CD4⁺/CD8⁺ ratio were greater than those with mean VL ≥1000 copies/mL ($p < 0.001$) (Table 2).

To identify the impact of HIV viremia persistence on CD4⁺ cell counts, the study population was classified as iLLV or pLLV. We found no significant difference in the mean CD4⁺ cell count, absolute CD4⁺ cell count, and the CD4⁺/CD8⁺ ratio between these two groups (Table 3). When analyzing the association between VCYs and CD4⁺ cell count, we discovered that the mean CD4⁺ cell count of patients with VCY ($\log_{10}$) <4 (577.7, IQR 429.2-736.7) was significantly higher than that of patients with VCY ($\log_{10}$) ≥4 (443.3, IQR 319.0-558.4) ($p < 0.001$).

We also performed logistic regression to identify the predictors of a mean CD4⁺ cell count ≥500 cells/μL during the study period. High CD4⁺ cell count at HIV diagnosis, not using integrase inhibitor as ART regimen, malignancy without history, lower mean VL, lower VCY, and high nadir CD4⁺ cell count were related to a mean CD4⁺ cell count ≥500 cells/μL in the univariate analysis. In the multivariate logistic regression analysis, we found the history of malignancy, VCY, and nadir CD4⁺ cell count as independent predictors (Table 4).

4. DISCUSSION

In this cohort study, among those with a mean VL <1000 copies/mL, there was a higher proportion of patients with a mean CD4⁺ cell count ≥500 cells/μL. The duration of HIV plasma VL of 50 to 1000 copies/mL did not influence the mean CD4⁺ cell count, CD4⁺ cell percentage, and CD4⁺/CD8⁺ ratio. Lewden et al revealed that when the patient's CD4⁺ cell count was ≥500 cells/μL on long-term cART, their mortality rates reached the same level as that of the general population.[17] Therefore, we performed univariate and multivariate analyses and indicated that the predictors of mean CD4⁺ cell count ≥500 cells/μL were malignancy without history, lower VCY, and high nadir CD4⁺ cell count.

The WHO suggests absolute CD4⁺ cell count rather than CD4⁺/CD8⁺ ratio as a standard for prophylaxis and preemptive treatment for pneumocystis pneumonia and invasive cryptococcal disease.[9] According to Ren et al, baseline CD4⁺ cell count was strongly inversely associated with survival in the first 6 months, whereas it becomes a weak prognostic factor after 6 months of starting ART.[18] This finding emphasizes the importance of baseline CD4⁺ cell count, similar to nadir CD4⁺ cell count, in the first 6 months. Esber et al demonstrated that compared with undetectable VL, pLLV ≥200 copies/mL doubled the risk of virologic failures.[6] Qin et al also revealed that the cumulative rates of VF in the LLV group (200 copies/mL < VL ≤ 400 copies/mL) and the nonsuppressed group were significantly higher than those in the viral-suppression group.[19] Mesic et al found an increased hazard for failure with age ≤19, baseline tuberculosis, and history of LLV (aHR 1.60; 95% CI: 1.42-1.81; $p < 0.001$).[20] According to Bernal et al, patients with LLV 200 to 499 copies/mL were more likely to develop virological failure and present AIDS cases or death in the long-term prognosis. In contrast, LLV 50 to 199 copies/mL was not associated with a higher risk of developing any of the above effects.[7] In our study, the mean CD4⁺ cell count

Table 1

Demographics and clinical characteristics of HIV-infected patients with different HIV viremia status

Variables	Virologic suppression n = 132 No. (%)	Low-level viremia n = 114 No. (%)	Virologic failure n = 185 No. (%)	*p*
Age, y, median (IQR)	40.0 (32.3-46.0)	38.0 (31.0-45.0)	34.0 (28.0-41.0)	0.001
Male	126 (95.5)	112 (98.2)	176 (95.1)	0.379
Underlying condition				
BMI	23.2 ± 3.6	23.4 ± 3.2	23.4 ± 3.6	0.819
Body weight	67.7 ± 12.5	67.6 ± 9.8	68.9 ± 12.1	0.529
Hepatitis B	16 (12.1)	15 (13.2)	20 (10.8)	0.824
Hepatitis C	20 (15.2)	15 (13.2)	33 (17.8)	0.561
Creatinine >1.5	16 (12.1)	14 (12.3)	26 (14.1)	0.850
Diabetes mellitus	14 (10.6)	10 (8.8)	14 (7.6)	0.646
Malignancy	12 (9.1)	5 (4.4)	10 (5.4)	0.253
opportunistic infections	24 (18)	20 (17.7)	58 (31)	0.005
HIV status				
$CD4^+$ count at HIV diagnosis, median (IQR)	246 (128-397)	255 (85-449)	308 (147-492)	0.222
Nadir $CD4^+$ count, median (IQR)	204 (77-307)	184 (58-313)	134 (59-246)	0.007
Mean $CD4^+$ count, median (IQR)	554 (393-734)	504 (360-668)	516 (413-668)	<0.001
Percentage of $CD4^+$ (%)	27.4 ± 7.1	27.3 ± 8.1	22.2 ± 6.7	<0.001
$CD4^+/CD8^+$ (%)	69.6 ± 30.2	72.0 ± 32.1	48.3 ± 21.3	<0.001
VL at HIV diagnosis, median (IQR)	50 100 (33 000-176 000)	89 950 (39 950-215 500)	31 200 (12 400-103 000)	0.300
Zenith VL, median (IQR)	55 850 (33 000-191 750)	94 400 (57 425-289 671)	91 900 (36 200-218 000)	0.542
Mean VL, median (IQR)	22 (20-26)	30 (26-40)	4064 (1108-13 305)	<0.001
VCY	2.4 ± 0.1	2.6 ± 0.1	4.7 ± 0.7	<0.001
Number of VL measurements/year	2.1 ± 0.4	2.2 ± 0.3	2.4 ± 0.7	<0.001
Major ART regimen				
NNRTI	65 (49.2)	53 (46.5)	74 (40.0)	0.237
PI	60 (45.5)	56 (49.1)	75 (40.5)	0.329
INSTI	7 (5.3)	5 (4.4)	33 (17.8)	<0.001

Data are presented as the mean ± SD, median (interquartile range [IQR]), or frequency with percentage (%).

ART = antiretroviral therapy; BMI = body mass index; HIV = human immunodeficiency virus; INSTI = integrase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; VCY = copy-years viremia; VL = viral load.

Table 2

Relationship of HIV plasma VL with absolute $CD4^+$ cell count, $CD4^+$ percentage, and $CD4^+/CD8^+$ ratio

Variables	Total (n = 431)	Mean VL <1000 (n = 290) No. (%)	Mean VL ≥1000 (n = 141) No. (%)	*p*
Mean $CD4^+$		603.4 ± 237.0	457.0 ± 178.4	<0.001
Mean $CD4^+$ <200	12	6 (2.1)	6 (4.3)	0.219
Mean $CD4^+$ <500	197	111 (38.3)	86 (61.0)	<0.001
Mean $CD4^+$ ≥ 500	234	179 (61.7)	55 (39.0)	<0.001
$CD4^+$ (%)		26.8 ± 7.5	21.8 ± 6.6	<0.001
$CD4^+/CD8^+$ (%)		68.1 ± 30.6	46.6 ± 20.5	<0.001

Data are presented as mean ± SD or frequency with percentage (%).

HIV = human immunodeficiency virus; VL = viral load.

Table 3

Relationship of duration of LLV with absolute $CD4^+$ cell count, $CD4^+$ percentage, and $CD4^+/CD8^+$ ratio

Variables	Total (n = 114)	iLLV (n = 69) No. (%)	pLLV (n = 45) No. (%)	*p*
Mean $CD4^+$		638.6 ± 188.5	607.6 ± 258.6	0.348
Mean $CD4^+$ <200	4	4 (5.8)	0 (0)	0.152
Mean $CD4^+$ <500	37	25 (36.2)	12 (26.7)	0.389
Mean $CD4^+$ ≥ 500	77	44 (63.8)	33 (73.3)	0.389
$CD4^+$ (%)		26.9 ± 8.7	28.0 ± 7.1	0.442
$CD4^+/CD8^+$ (%)		70.5 ± 34.4	74.2 ± 28.7	0.315

Data are presented as mean ± SD or frequency with percentage (%).

LLV = low-level viremia.

Table 4

Logistic regression analysis of potential predictors of mean CD4⁺ cell counts ≥500 cells/μL for HIV-infected patients

Variables	Mean CD4⁺ <500 N = 197 No. (%)	Mean CD4⁺ ≥500 N = 234 No. (%)	Univariate analysis *p*	Multivariate analysis Odds ratio (95% CI)	*p*
Age, y, median (IQR)	37 (30-46)	36 (30-42)	0.134		
Male	187 (94.9)	227 (97.0)	0.273		
Hepatitis					
Hepatitis B	26 (13.2)	25 (10.7)	0.422		
Hepatitis C	33 (16.8)	35 (15.0)	0.611		
Diabetes mellitus	21 (10.7)	17 (7.3)	0.218		
Malignancy	20 (10.2)	7 (3.0)	0.004	0.22 (0.06-0.76)	0.017
Opportunistic infections	72 (36.5)	30 (12.8)	<0.001	0.74 (0.41-1.34)	0.318
HIV status					
VL at HIV diagnosis, median (IQR)	55 900 (19 350-20 9500)	50 900 (28 300-111 000)	0.837		
Zenith VL, median (IQR)	102 000 (42 900-323 500)	72 903 (33 000-188 250)	0.974		
Mean VL, median (IQR)	395 (25-6250)	32 (25-741)	0.001	1.00 (1.00-1.00)	0.803
VCY	3.5 ± 1.3	3.0 ± 1.0	<0.001	0.40 (0.22-0.74)	0.003
CD4⁺ count at HIV diagnosis, median (IQR)	195 (63-310)	374 (210-564)	<0.001	1.00 (1.00-1.00)	0.453
Nadir CD4⁺ count, median (IQR)	83 (29-175)	252 (146-384)	<0.001	1.01 (1.01-1.01)	<0.001
ART regimen					
NNRTI	87 (44.2)	105 (44.9)	0.883		
PI	82 (41.6)	109 (46.6)	0.302		
INSTI	28 (14.2)	17 (7.3)	0.021	0.72 (0.32-1.63)	0.434

Data are presented as mean ± (SD), median (interquartile range [IQR]), or frequency with percentage (%).

ART = antiretroviral therapy; CI = confidence interval; HIV = human immunodeficiency virus; INSTI = integrase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; VCY = copy-years viremia; VL = viral load.

of patients with mean VL <1000 copies/mL was significantly higher than those with mean VL ≥1000 copies/mL. However, predictors of mean CD4⁺ cell count ≥500 cells/μL included only malignancy without history, lower VCY, and high nadir CD4⁺ cell count. Mugavero et al demonstrated a strong association between VCY and mortality has been reported among patients on ART.[21] Therefore, frequent VL testing should be considered in these patients. These findings were compatible with those of Castillo-Mancilla et al, showing a possible relationship between treatment adherence and LLV.[22]

We found that the integrase inhibitor was not a predictor of a mean CD4⁺ cell count ≥500 cells/μL. Changing the ART regimen might not be helpful in the setting of LLV.[10] The U.S. DHHS guidelines indicated that management of LLV should be individualized and the first step is to assess and address adherence, potential drug-food interactions (including interactions with supplements), and drug-drug interactions. Moreover, patients with HIV plasma VL levels between the lower limits of detection and 200 copies/mL did not require a change in treatment. The risk of developing resistance is believed to be relatively low.[10]

This study has some limitations. First, clinical data were collected from pure medical records based on a hospital-based study design. Second, HIV plasma VL testing was performed every 3 to 6 months. The frequency of testing might not represent the total HIV plasma VL exposure. Therefore, we calculated VCY to further evaluate the influence of VL exposure in the LLV setting. Third, this was a tertiary medical center study in northern Taiwan, with participants primarily having male sex and MSM. Despite these limitations, this was a long-term retrospective cohort study that may provide useful information on LLV in HIV-infected patients.

In conclusion, the mean CD4⁺ cell count ≥500 cells/μL in HIV-infected patients was not influenced by LLV duration. Using an integrase inhibitor as an ART regimen, a history of hepatitis B, hepatitis C, and diabetes mellitus were not independent predictors of mean CD4⁺ cell counts ≥500 cells/μL. Patients with a history of malignancy, high VCY, and low nadir CD4⁺ cell counts should be monitored carefully in clinical settings. These findings should be further verified with large randomized studies.

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