

## RESEARCH ARTICLE

# Potential of Interleukin 7 (IL-7) and CD4/CD8 Ratio as Markers of Immune Reconstitution in HIV Patients on Antiretroviral Therapy in Yaoundé, Cameroon

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## Abstract

**Background:** Although plasma viral load is the main indicator of viral progression amongst HIV-infected patients on antiretroviral therapy, immune reconstitution remains a major challenge, as using absolute CD4 T-cells as a marker of disease progression and status remains controversial. Our study aimed to evaluate the potential of interleukin 7 (IL-7) and CD4/CD8 ratio as markers of immune reconstitution amongst HIV patients on antiretroviral therapy (ART) in Yaoundé, Cameroon.

**Methods:** In a cross-sectional study conducted from July to December 2017, at the Yaoundé University Teaching Hospital, we enrolled 200 participants. T-lymphocyte profile, IL-7 level and plasma viral load were determined using whole blood and plasma specimens by standard methods. Graph Pad Prism 5.0 and Epi Info 7.0 software were used for statistical analysis. Comparisons between IL-7 plasma level, CD4/CD8, CD4+T-cells and viral load within the different groups, were performed using the non-parametric Kruskal Wallis test. The correlations between IL-7, CD4/CD8 ratio, CD4+T-cells and HIV loads were established using the Spearman's correlation coefficient.

**Results:** Enrolled participants were divided into three groups: ART success 110 (54%), ART failure 58 (30%) and Uninfected 32 (16%). The mean age of treatment was  $3 \pm 0.76$  years. The plasma level of IL7 and CD4/CD8 ratio were statistically different between the three groups with  $p < 0.0001$ . There was a direct correlation between IL-7 and viral load ( $r = 0.6$ ;  $p = 0.03$ ; 95% CI = [0.02005 to 0.8952]). It was inverse between IL-7 and CD4 lymphocytes ( $r = -0.7$ ;  $p = 0.03$ ; 95% CI = [-0.93 to 0.26]). There was an inverse correlation between CD4/CD8 ratio and viral load ( $r = -0.8$ ;  $p = 0.004$ ; 95%CI = [-0.9302 to -0.3887]) and between IL-7 and CD4 / CD8 ratio ( $r = -0.7$ ;  $p = 0.01$ ; 95% CI = [-0.9255 to -0.1961]).

**Conclusion:** The variation in CD4/CD8 ratio and the level of IL-7 was statistically significant amongst ART failure and success patients. IL-7 and CD4/CD8 ratio were influenced by ART in both groups. They might be predictive of immunological dysfunction associated to the disease progression and then might be used as immunological markers in the immunological monitoring of HIV infected patients.

**Keywords:** Interleukin 7; CD4/CD8 ratio; ART success; ART failure

## Introduction

HIV infection is essentially an immune system infection, targeting CD4+ T-cells cells which are central coordinators of B and T adaptive responses against intracellular pathogens [1]. In the body, HIV will, under certain conditions, lead to severe immunosuppression, causing Acquired Immunodeficiency Syndrome known as AIDS [2]. The innate and adaptive immunological response to primary infection is crucial for the control of HIV replication [3]. During the progression of the infection, the persistence of low CD4/CD8 ratio is predictive of morbid events independent of the virus, and that the inversion of that ratio is link to the chronic T-lymphocyte activation [4]. This indicates the critical role played by the ratio in the process of immune reconstitution,

suggesting the necessity for its surveillance [5]. A cytokine called Interleukin 7 (IL-7) plays a prominent role in the immune response to viral infections. It acts in the primary stage, stimulating the proliferation of T-cells. Its high blood level in HIV-infected patients is associated with lymphopenia [6]. IL-7 also plays a critical role in the survival of naïve and memory T-cells [7]. It acts in the differentiation, the proliferation of B and T-cells, the regulation of the cooperation between the B and T-cells as well as their effector function [8,9]. Several studies have shown that antiretroviral therapy (ART) is intended to lead to virologic suppression and improve immune function, thereby reducing the incidence of AIDS-related infection and mortality [10]. This implies the need for monitoring of virological progression and immune reconstitution. Although viral load is the main marker for monitoring viral replication, it does not provide information on the immunological state of patients [1]. Absolute CD4 T-lymphocyte has long been used as an immunological marker to control immunological reconstitution. However, its use remains open for discussion, as there are needs of alternative approaches to immunological monitoring. The aim of our study was to evaluate the potential of IL-7 and CD4/CD8 ratio amongst HIV treated and untreated patients on ART in Yaoundé, Cameroon.

## Materials and Methods

### Study Design and Ethical Consideration

We conducted a cross-sectional study from July to December 2017, at the agreed HIV care center of Internal Medicine unit of the Yaoundé University Teaching Hospital from daily consultation by physicians. We enrolled HIV uninfected and infected (ART failure and ART success) individuals aged more than 18 years. Untreated patients and those on treatment for less than one year were excluded. Patients were receiving a standard first line ART regimen which includes the combination of two nucleoside reverse transcriptase inhibitors (NRTIs), chosen among Zidovudine (AZT), Tenofovir (TDF) and Lamivudine (3TC) and a non-nucleoside reverse transcriptase inhibitor (NNRTI), being either Efavirenz (EFV) or Nevirapine (NVP) for at least one year.

ART Success and ART Failure was defined using the WHO definition [11]: Treatment success (viral load <1000 copies/ml, CD4>500 cells/ $\mu$ l and duration under ART for at least 6months,) and Failure (viral load >1000 copies/ml with CD4<200 cells/ $\mu$ l based on two consecutive viral load measurements after 3 months, with adherence support). A standard questionnaire was used to capture demographic characteristics and clinical information of patients. These included age, sex, ART regimen and duration on ART.

We obtained an ethical clearance from the Cameroon National Ethical committee (reference number 044/CNE/SE/2017). Written and verbal informed consent was given by all participants. The study was conducted according to the ethical guidelines and principles of the international Declaration of Helsinki 2013.

### Specimens

Whole blood (3 to 5 ml) was obtained by venipuncture at the bend of the elbow in EDTA anticoagulant tubes at the sample collection unit of the Yaoundé University Teaching Hospital. Samples were transported at the Center for the Study and Control of Communicable Diseases (CSCCD) of the Faculty of Medicine and Biomedical Sciences (FMBS) of the University of Yaoundé I for storage and analyses. The plasma was obtained by the centrifugation of whole blood at 5000rpm for 5 minutes and stored in cryo vials at -20 °C.

### T-Lymphocyte phenotyping

The measurement of CD4+/CD3+ and CD8+/CD3+ T-lymphocytes was done based on the principle of immunophenotyping. Fifty microliters (50 $\mu$ L) of whole blood was used for the analyses using the DB FACS Count Reagent kit, automated machine (BD Biosciences, San Jose, California, USA). Samples, including quality controls, were analyzed based on the manufacturers' guidelines.

### Measurement of plasma level of interleukin 7

Plasma level of IL-7 was measured using quantitative sandwich Enzyme-linked Immune-Sorbent Assay (ELISA) kits (Invitrogen, Thermo Fisher Scientific, USA). A solid-phase Immune-Enzymatic technique was used on a microtiter plate for the quantitative determination of IL-7 in human plasma. Samples were analyzed according to the manufacturer's specifications. The absorbance was read using a spectrophotometer (Biotech ELx800, USA) set at a dual wavelength of 450 and 550nm. Each sample was run in duplicate. The concentration was determined by extrapolating the results from a standard curve generated by plotting the average absorbance (450 and 550nm) obtained for each standard level on the vertical (Y) axis compared to the corresponding IL-7 concentration on the horizontal (X) axis.

### Measurement of viral load

Determination of the viral load was performed using the Cobas Ampliprep / Cobas Taqman 96 platform (Roche Diagnostics Branchburg, New Jersey USA) strictly using the manufacturer's instructions. The detection limit was <40 copies/ml.

### Statistical analyzes

Data were analyzed using the Epi Info 7.0 software (Epi Info™, DHIS, CSELS, CDC, 1600 Clifton Road Atlanta, GA 30329-4027 USA) and Graph Pad PRISM 5.0 software package (Graph Pad Software Inc., La Jolla, California, USA). Comparisons between IL-7

plasma level, CD4/CD8, CD4+T-cells and viral load within the different groups, were performed using the non-parametric test of Kruskal Wallis. The Dunn's post test was performed to compare all pairs of groups. The correlations between IL-7, CD4/CD8 ratio, CD4+T-cells and HIV loads were established using the Spearman's correlation coefficient (r). Any value of  $p < 0.05$  was considered statistically significant for a 95% confidence interval.

## Results

### Socio-demographic and clinical characteristics

Of the 200 participants enrolled in our study, 37 (25%) were men and 163(75%) were women. The participant's age ranged from 18 to 60 with a median of 39 years old (Table 1). Our study population was divided into three groups: ART success 110 (54%), ART failure 58 (30%) and Uninfected 32 (16%) (Table1).

Characteristics		n (%)
Sex	Male	37 (25)
	Female	163 (75)
Groups	Uninfected	32 (16)
	Failing ART	58 (30)
	ART success	110 (54)
Age (years)	Median (range)	39 (18 -60)
Duration on treatment (years) ART Success	Median (range)	2.5 (1-8)
Duration on treatment (years) ART Failure	Median (range)	3 (1-8)

Table 1: Socio-demographics and clinical characteristics

### Comparison of IL-7 between groups

Plasma concentration of IL7 ranged from 17.64 to 51.76 (median: 41.48) pg/ml in ART failure; 9.40 to 37.63 (median: 24.78)pg/ml in ART success and 6.80 to 27.35 (median: 17.35) pg/ml in uninfected group. The difference was statistically significant between the three groups with  $p < 0.0001$  (Figure 1).

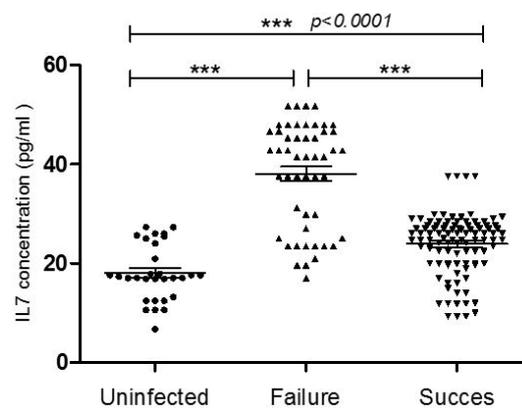


Figure 1: IL-7 plasma level amongst ART Failure, ART Success and patients uninfected by HIV

### Comparison of CD4/CD8 ratio between groups

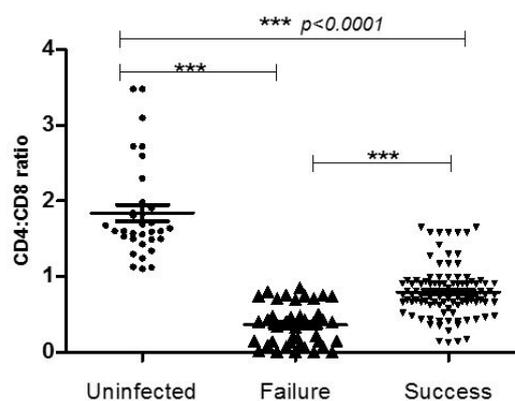


Figure 2: CD4/CD8 ratio between ART Failure, ART Success and patients uninfected by HIV

CD4/CD8 ratio ranged from 0.01 to 0.85 (median: 0.34) in ART failure, 0.13 to 1.65 (median: 0.76) in ART success and 1.10 to 3.48 (median: 1.68) in uninfected group. The difference was statistically significant between the three groups with  $p < 0.0001$  (Figure 2).

### Comparison of CD4 T-Lymphocytes between groups

CD4 T-Lymphocytes count ranged from 3 to 200 (median: 160.5) cells/ml in ART failure, 500 to 1673 (median: 700) cells/ml in ART success and 614- 1930 (median: 993) cells/ml in uninfected group. The difference was statistically significant between the three groups with  $p < 0.0001$  (Figure 3).

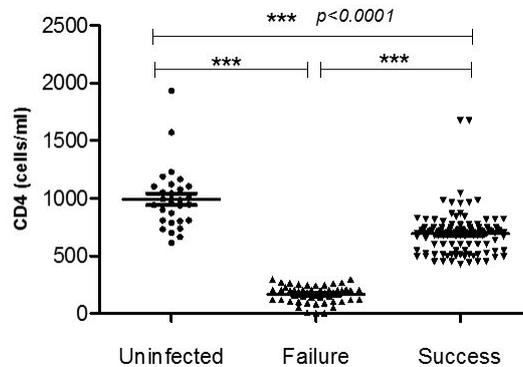


Figure 3: CD4 T-Lymphocytes within ART Failure, ART Success and patients uninfected by HIV

### Comparison of viral load between groups

Viral load ranged from 2043 to 72400 (median: 40020) copies/ml in ART failure and 40-1000 (median: 240) copies/ml in ART success group. The difference was statistically significant with  $p < 0.0001$  (Figure 4).

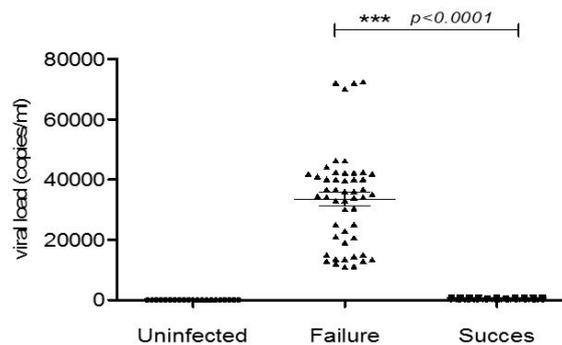


Figure 4: Plasma level of viral load within ART Failure, ART Success and patients uninfected by HIV

### Correlation between IL7, CD4 / CD8 ratio and viral load

There was an inverse association between IL-7 plasma level and CD4 T-Lymphocytes with a spearman correlation coefficient of  $r = -0.7$  ( $p = 0.03$ , 95% CI = [-0.93 to 0.26]). The association was inverse between IL-7 plasma level and CD4 T-Lymphocytes with spearman correlation coefficient of  $r = -0.6$  ( $p = 0.01$ , 95% CI = [-0.90 to -0.27]) (Table 2). The correlation was direct between IL-7 and viral load with a spearman correlation coefficient of  $r = 0.6$  ( $p = 0.03$ , 95% CI = [0.02005 to 0.8952]). There was an inverse association between CD4/CD8 ratio and viral load with a spearman correlation coefficient of  $r = -0.8$  ( $p = 0.004$ , 95% CI = [0.9302 to -0.3887]) and  $r = -0.7$  ( $p = 0.03$ , 95% CI = [-0.9119 to -0.0569]). The correlation was inversely correlated between the IL-7 concentration and the CD4/CD8 ratio in people with treatment success with a correlation coefficient  $r = -0.7$  ( $p = 0.01$ , 95% CI = [-0, 9255 to -0.1961]) (Table 2).

	IL7	CD4	Ratio CD4/CD8	Charge Virale
IL7		-0,7**	-0,7**	0,6*
CD4	-0,7**		0,5	-0,8**
Ratio CD4/CD8	-0,7**	0,5		-0,8***
Charge Virale	0,6*	-0,8**	-0,8***	

Table 2: Correlation between IL7, CD4 / CD8 ratio and viral load

## Discussion

Plasma IL7 concentration was statistically elevated in HIV-infected individuals and was statistically associated with HIV load. Compared to ART success patients, ART failure patients had a higher level of IL-7. IL-7 is involved in lymphopoiesis and peripheral

lymphocyte homeostasis [8]. Under normal conditions (non-infection), IL-7 promotes the survival of naïve and memory T-cells without inducing proliferation, but by maintaining the pool of that cell type and the stable cytokine network. HIV infection causes deregulation of the body's cytokine profile in response to immune dysfunction and mostly lymphopenia. By acting at several levels of the immune system, IL-7 seeks to restore impaired balance during infection [12,13]. We realize that in our study the elevated plasma level of IL-7 is strongly associated with disease progression. Compared to uninfected individuals, IL7 plasma level remain higher in people with ART success reflecting an incomplete immune reconstitution although the virological success. Viral replication is thought to be more important in people who are failing ART, putting more stress on the immune system, hence the large production of IL-7. This production begins to decrease significantly after taking antiretroviral drugs, indicating a progressive reconstitution of immune dysfunctions caused by HIV. IL-7 would therefore have a significant inhibitory effect on viral replication [12] and a satisfactory homeostatic impact on the T-cell repertoire, when using as complementary to ART [14,15].

The inverse association between IL-7 and CD4 T-Lymphocytes in our study confirms the fact that HIV infection leads to lymphopenia depending on the virologic stage [16,17]. That lymphopenia rapidly stimulates the production of IL-7, which is the main regulator of CD4 T-cells homeostasis, which may also be indicative of viral progression [18,19]. IL-7 selectively induces the proliferation of naïve and memory T-cells. In addition, depending on the degree of lymphopenia, it can contribute to the formation of naïve cells with the characteristics of memory cells [20,19]. Some authors [21] in their work on immune system activation pathways in HIV infection have shown that IL-7 is elevated in patients with VL > 1000 copies/ml compared to those in virological suppression. This result goes in the same line as ours where there was a direct association between IL-7 and viral load. Indeed, viremia associated with HIV infection maintains and perpetuates an inflammatory environment in the human body. It causes by this fact under certain conditions, a spectacular effect mediated by cytokines and mainly IL7. Inflammation leads to lymphopoiesis and proliferation of CD4 and CD8 T-cells via this cytokine. This effect is attenuated with virological suppression suggesting the influence of viral load on plasma IL7 concentration [21].

CD4/CD8 Ratio was high in HIV uninfected and treatment success participants when compared with those infected and those with treatment failures. These results are showing the persistent activation of the immune system during the pathogenesis of HIV which has been identified as a major contributor of immunological failure [22,23]. This could be a result of the inflammatory response to HIV and the homeostatic response to CD4 T cell depletion. The optimal lymphocyte recovery is closely dependent on the number of cells at initiation and the duration of ART [24]. In addition, the proliferative capacity and activation status of T cells during acute and chronic HIV infection are predictive of disease progression [25]. The low CD4/CD8 ratio is often associated with reconstitution or non-reconstitution of the immune system giving indications of progression to AIDS and non AIDS diseases [20]. The CD4/CD8 ratio represents a combined effect of inflammation and immunological changes. However, the mechanism underlining partial ratio recovery during long-term antiretroviral therapy remains poorly understood. It has recently been indicated that patients who have achieved optimal CD4 coverage but low CD4/CD8 ratio, are at high risk of developing non-AIDS diseases because of the persistence of immune system activation. In addition, persistent elevation of CD8 LT during HIV pathogenesis is thought to be a low ratio. This elevation is predominant in ART-naïve individuals and would continue in the long-term ART [26]. For some, LTCD8 may reveal the link between HIV progression and the time needed to normalize the CD4/CD8 ratio [5]. Interleukin 7 is often referred to as an agent of immuno-reconstitution in various forms of immunodeficiency and particularly that induced by HIV. This cytokine has a proliferative effect on both CD4 T cells and is associated with a diversification of the repertoire of T cell receptors. The inversion of the immunological balance would be at the origin of a greater expression of IL-7 in patients on ART [27]. This also corroborates our results where the plasma concentration of IL-7 was inversely associated with the CD4/CD8 ratio. However, only 20% of virological success patients have immunologically reconstituted based on CD4/CD8 ratio. This indicates the critical role of the CD4/CD8 ratio in antiretroviral therapy monitoring. Therefore, the expected viral progression cannot be an indicator of the immunological status of patients on antiretroviral therapy.

We could obtain more precise results doing a longitudinal study to measure the interleukin 7 concentration at different points of time according to the half-life, and the immune reconstitution process for each consent participant. We plan to do another study to determine the implication mechanism of IL7 in the persistent activation of T cells and cells aging in HIV infected individuals.

## Conclusion

The variation in CD4/CD8 ratio and the level of IL7 was statistically significant between uninfected and treated individuals. IL7 and CD4/CD8 ratio were influenced by the treatment response (failure and success). They might be predictive of immunological dysfunction associated to the disease progression and then might be used as immunological markers in the immunological monitoring of HIV infected patients.

## Conflicts of interest

All the authors to this paper declare no conflict of interest in this work.

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## Author's contribution

**CHM and GMI:** Development of research concept, recruitment of patients, Laboratory analyses, interpretation of results and participated in the initial draft of the manuscript. **GBJ and OAMC:** Development of research concept, interpretation of results and drafting of manuscript. **MM, CT and EL** contributed in laboratory analyses and drafting of the manuscript. All authors read and approved the final version of the manuscript.

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