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A Longitudinal study on the Kinetic of T-cells and certain hematological parameters during the Initiation of antiretroviral therapy and after two years on treatment

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Abstract

Background: T- cell are key regulators of the immune system and their role in the initiating and follow –up of patients on antiretroviral therapy (ART) is primordial. In the present work, we compared T-cells and certain biological parameters after 2 months of ART with those obtained after one year and 2 years of ART.

Method: In this prospective cohort study, 150 HIV patients on primo ART treatment and consenting were recruited. Five ml of blood were collected at initiation (M0), after 2 months (M2), after 1 year (M12), and after 2 years (M24) of ART. CD4 cells, CD8 cells, and other hematological parameters were measured according to standard operating procedures.

Results: The 88 retained participants included 18 (20.6%) men and 70 (79.4%) women, with a mean age of 35.5 years. After 2 months, there was a significant increase in CD4 count, monocytes, and platelets with p-values of 0.001, 0.02, and 0.04, respectively, while hemoglobin and CD8 cells did not significantly change (p-values of 0.06 and 0.82, respectively). After one year and after two years of therapy, the increases in these parameters were not statistically significant compared to the values obtained at M2.

Conclusion: CD4 lymphopenia, monopénia and thrombopenia induced by HIV infection are corrected maximally during the first months after the beginning of ART and tend to stabilize over time, while anemia can continue to persist.

Keywords: HIV; ART; Monocytopenia; Lymphopenia; Thrombopenia

1 Introduction

In 2022, the Common Program of the United Nations on HIV/AIDS (UNAIDS) estimated that almost 70% of the 39 million people infected with human immunodeficiency virus (HIV) worldwide live in Africa [1].

The infection with HIV begins with the fixation of gp-120 on the CD4 molecule, and then the fusion of the virus envelope to the cell membrane through the co-receptors CXCR4 and CCR5 allows the penetration of the viral RNA into the cell. The CD4 lymphocytes recognize the protein antigen of the virus and secrete interleukins that stimulate monocytes, CD8, and B lymphocytes [2]. The viral replication results in a significant destruction of the defense mechanisms, particularly

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cellular-dependent immunity [2, 3]. The persistence of viral replication strongly activates immunity and induces profound immunosuppression that settles gradually.

The cellular immunosuppression is multifactorial and is due either to the direct cytopathic effect of HIV or to the cytotoxic CD8 response against infected CD4 cells, or to the phenomena of apoptosis and a decrease in thymic regeneration [2, 4]. Primary infection is thus marked by deep CD4 lymphocyte depletion, with destruction within a few weeks of more than 80% of CD4 T lymphocytes in the organism. The chronic phase is characterized by viral replication relative control through the establishment of strong, specific cytotoxic T CD8 responses. These CD8 T cells play a major role in enabling a significant reduction in viral replication by killing cells in which the virus replicates. CD8 cells also release granzyme and a serine protein that enters the pores caused by perforin and induces apoptosis. These abnormalities are the cause of a deep deficit, in particular in specific cellular immunity (CD4 Th1) and nonspecific immunity (monocytes and macrophages), which are key elements of the defense against intracellular pathogens such as Mycobacterium or Cryptococcus. Indeed, the strong activation of immunity causes a significant increase in the rest energy associated with malnutrition, leading to hematologic abnormalities such as anemia. [5, 6].

The triple antiretroviral therapy (ART) combination has led to a major decline in morbidity and mortality during HIV infection. These antiretroviral treatments allow an important suppression of viral replication and a restoration of at least partial immune responses, both quantitatively and qualitatively [7]. Immune reconstitution evolves in two phases: an early phase in the first two to three months, often with a rapid increase in CD4 cell count, reflecting the reallocation of memory CD4 lymphocytes sequestered in lymphoid organs, followed by a stage of slow regeneration of naive CD4 [7, 8]. Meanwhile, the suppression of viral replication leads to decreased activation of the immune system and of the apoptosis phenomenon [7]. These effects allow the rapid reappearance of specific immunity directed against environmental antigens [9, 10], but also against the antigens of infectious agents responsible for opportunistic infections [11, 12]. However, new preoccupations arise from the initiation of ART and the worsening of the clinical condition of patients. These complications of ARTs, within various mechanisms related to the virus itself, opportunistic infections affecting the hematopoietic organs [13] or secondary affections due to drug toxicity [14], become major issues for monitoring patients on ART. The maculopapular rash is the most common form of drug eruption in patients infected with HIV (75% of cases), with an onset within 10 days on average. The Stevens-Johnson and Lyell syndromes are toxic epidermal necrolysis, with a mortality rate ranging from 5% for Stevens-Johnson syndrome to 30% for Lyell [15]. The hypersensitivity syndrome is a severe form of drug eruption involving a severe rash and visceral affection, worsening the prognosis in 10% of cases associated with biologic abnormalities. It occurs in slightly more than half of patients within two to six weeks after the initiation of ART. [16, 17]. The hematological complications with reverse transcriptase inhibitors (RTINs), which have myelosuppressor effects, especially zidovudine, often lead to anemia [18, 19]. The complications related to immune restoration inflammatory syndrome include a set of pathological manifestations related to immune reconstitution following the implementation of ART or exacerbations of pre-existing infectious disease generally occurring in the first two months of ART [20]. These disorders are further found in the first two months of ART, thus complicating the management of HIV infection. Our study aimed at evaluating the changes of T-cells and certain blood parameters (monocytes, hemoglobin, and platelets) after 2 months compared to the changes at one year and those of 2 years after initiation of ART.

2 Method

2.1 Participants and Study setting

The recruitment of patients was undertaken at the Yaoundé Jamot Hospital (YJH) in a specialized treatment center for HIV, the *Centre de Traitement Agrée (CTA).* As inclusion criteria, HIV-1-positive patients initiating anti-retroviral therapy (ART) were consecutively enrolled.

One hundred and fifty HIV-positive patients were eligible for the study; they were diagnosed HIV-1-positive at the YJH and eligible to start ART therapy. 88 remained in the study until two years (M24), and others were lost to follow-up during the study period. ART therapy in HIV-positive patients in Cameroon is carried out through a weekly appointment under appropriate medical supervision, especially during the first two months after the initiation of ART. The classic therapeutic strategies for HIV were standardized and constituted of three molecules (Tenofovir + Lamivudine + Efavirenz) or (Zidovudine + Lamivudine + Efavirenz).

2.2 Material and procedure

HIV patients were identified every Friday by the CTA. Friday was chosen by medical staff to initiate ART for eligible HIV patients. Patients fulfilling the inclusion criteria gave their written consent to participate in the study.

Demographic characteristics (age, gender) were collected. Various paramedical parameters were collected from their medical records. The clinical state of participants was monitored at baseline (M_0), after two months (M2), after one year (M12), and after two years (M_{24}) of antiretroviral (ARV) therapy.

This was a prospective cohort study carried out over two years (from January 2013 to December 2015). Five milliliters of venous blood in EDTA tubes were collected from each patient at M_0, M_2, M12, and M_{24} using standard blood collection procedures. The samples were transported to the Centre for the Study and Control of Communicable Diseases (CSCCD) laboratory of the Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, where they were analyzed within 6 hours of collection. The quantification of CD4 and CD8 cells was done using the FACSCount machine (Becton, Dickinson; Belgium); hematological parameters (total lymphocytes, monocytes, hemoglobin, and platelets) were measured using an automated CELL-DYN 3200 (Abbott; France); and a thin blood smear was read by standard microscopy. All samples were analyzed strictly according to the manufacturer's guidelines.

2.3 Ethical considerations

Ethical clearance for this study was obtained from the Cameroon National Ethics Committee of Research for Human Health (N° 237/CNE/SE/2012). Participation in this study was voluntary. A signed consent form was sought from all participants. Standard procedures were used and involved minimal risk for the participants. The study results were returned to the patients and incorporated into their medical records.

2.4 Data Analysis

Data collected during this study were entered into SPSS (Statistical Package for Social Sciences) version 15. Qualitative variables were represented as frequencies and proportions. Quantitative variables were presented as mean ± standard deviation. The chi-square or Fischer test was used to compare proportions. The student T-test and its non-parametric equivalent were used to compare means or medians. For p-values below 0.05, the difference was considered statistically significant with a confidence interval of 95%.

3 Results

3.1 Demographic and clinical characteristics

A total of 88 participants were retained for the study, comprising 70 (79.4%) females and 18 (20.6%) males. The study population was 23 to 58 years old. In these patients, the median age was 33 years, with the age range [25–39] years being the most represented. These patients initiated ART made up of Zidovudine (AZT), Lamuvudine (3TC), and Efavirenz (EFV).

3.2 The significant increase of blood parameters between M_0 and M_2 (Table 1)

After two months of ART (M_2), we observed a statistically significant increase of: mean (±SD) CD4 in patients from 178.15 (± 50) to 340.68 (± 153) /mm^3 ($p < 0.001$), CD4/CD8 ratio (±SD) from 0.22 (±0.03) to 0.40 (± 0.3) with $p < 0.001$), mean (± SD) monocytes from 109.84 (± 73) to 316 (± 140) /mm3, and platelet count from 118110.64 (± 20255) to 223424.2 (± 11756) /mm^3.

Table 1 Increase of blood parameters between M_0 and M_2

Parameters	**M_0**	**M_2**	**P**
CD4 (±SD)/mm^3	178.15 ± 50	340.68 ±153	0.001
CD8 (±SD)/mm^3	1086.64 ± 600	1044.67 ± 553	0.82
CD4/CD8 (±SD)	0.22 ± 0,03	0.40 ± 0.3	0.001
Monocytes (±SD)/mm^3	109.84 ± 73	301.60 ± 140	0.02
Lymphocytes (±SD)/mm^3	1828.36 ± 130	1987.57 ± 242	0.13
Hemoglobin (±SD) g/dL	10.50 ± 0,32	11.31 ± 0.30	0.06
Platelets (±SD)/mm^3	118110.64 ± 20255	223424.2 ± 11756	0.04

There was no significant change in the levels of CD8 cells, total lymphocytes, or hemoglobin, with p values of 0.82, 0.13, and 0.06, respectively.

3.3 Comparison of blood parameters between M_2 and M_{12}: (Table 2)

From M_2 to M_{12}, the increase of all parameters was not statistically significant except the value of the CD4/CD8 ratio (p = 0.03) compared to M_2.

Table 2 Kinetic of blood parameters between M_2 and M_{12}

Parameters	M_2	M_{12}	p
CD4 (±SD)/mm^3	340.68 ±153	400.17 ± 36.46	0.08
CD8 (±SD)/mm^3	1044.67 ± 553	1001.63 ± 653	0.50
CD4/CD8 (±SD)	0.40 ± 0.3	0.52 ± 0.72	0.03
Monocytes (±SD)/mm^3	301.60 ± 15.53	313.52 ±33	0.30
Lymphocytes (±SD)/mm^3	1987.57 ± 242	1967.58 ± 110	0.94
Hemoglobin (±SD) g/dL	11.31 ± 0.30	11.47 ± 0.27	0.40
Platelets (±SD)/mm^3	223424.2 ± 11756	229755.3 ±16708	0.09

3.4 Comparison of blood parameters between M_2 and M_{24} (Table 3)

Even after M_{24}, there was no statistically significant change in the levels of parameters except for the CD4/CD8 ratio.

Table 3 Kinetic of blood parameters between M_2 and M_{24}

Parameters	M2	M24	p
CD4 (±SD)/mm3	340.68 ±153	415.97 ± 196	0.08
CD8 (±SD)/mm3	1044.67 ± 553	984.73 ± 321	0.40
CD4/CD8 (±SD)	0.40 ± 0.3	0.63 ± 0.32	0.03
Monocytes (±SD)/mm3	301.60 ± 140	333.51 ± 143	0.3
Lymphocytes (±SD)/mm3	1987.57 ± 242	1967.58 ± 210	0.94
Hemoglobin (±SD) g/dL	11.31 ± 0.30	11.67 ± 0.27	0.38
Platelets (±SD)/mm3	223424.2 ± 11756	229735.3 ±16708	0.09

3.5 Comparing the mean increase between M_0-M_2 period and M_2-M_{24} period (Table 4)

Table 4 Comparing the increase of M_2-Mo to M_{24}-M_2 period

Biologic parameters	Difference M_2-M_0	Difference M_{24} – M_2	P
CD4 (±SD)/mm^3	+ 162.53 (100)	+75.29 (78.5)	0.004
CD8 (±SD)/mm^3	- 46.07 (49.5)	-59.94 60)	0.07
CD4/CD8 (±SD)	+ 0.18 (0.22)	0.13 (0.14)	0.8
Monocytes (±SD)/mm^3	+191.76 (105)	+31.91 (26,3)	0.02
Lymphocytes (±SD)/mm^3	+159.57 (200)	-19.99 (30.1)	0.03
Hémoglobine (±SD) g/dL	0.81 (1.30)	0.36 (0.32)	0.07
Platelets (±SD)/mm^3	105313.56 (3764)	6311.10 (2341)	0.04

CD4 cells increased faster for the M_0-M_2 period by +162.53/mm3 as compared to the period from M_2-M_{24} (+75.29/mm3), p-value of 0.004. Monocytes increased much faster for the M0-M2 period by +191.76/mm3 than from M_2-M_{24} with only +31.91/mm3 (p = 0.02). Platelet count also increased faster for the M_0 to M_2 period (+ 105313.56/mm^3) compared to M_2 to M_{24} with an increase of only + 6311.10/mm^3 (p-value = 0.04). Regarding other parameters, there were no statistically significant differences in the variation of these parameters between the two periods.

4 Discussion

ARV combination therapy significantly slows viral replication and therefore prevents infection of new cells. The immune system can then react against preexisting opportunistic infections, and there is a reactivation and proliferation of specific immune cells such as CD4 and non-specific immune cells such as monocytes initiated to master these infections. This could justify the significant increase in CD4 and monocytes at the beginning of ARV therapy in the first two months. It would thus be an inflammatory syndrome due to the reactivation of the immune system associated with pre-existing infections before starting ARV therapy. With the continuous intake of ARVs, opportunistic infections regress [21]; the immune system does not need to be reactivated, hence the non-significant increase of CD4 cells and monocytes after two years compared to two months of treatment.

The CD8 level remains high before and during ART and is justified by the fact that the CD8 cells are not a target of HIV. In addition, CD8 are cytotoxic cells having a very important role in the control of viral replication [22]; their clonal expansion is continuous with the aim of eliminating cells infected by HIV. While some studies suggest that the initial expansion of CD8 is transient and disappears within six months after the primary HIV infection phase [23, 24], other longitudinal studies show an expansion of CD8 long after the primary infection [22]. Our data on HIV patients on treatment confirms the persistence of CD8 cells until two years after the initiation of ARV therapy.

Otherwise, the significant increase in the CD4/CD8 ratio after M_2 and over time is certainly due to an increase in CD4 counts and also to the slow decrease rate of CD8 cells, although this was not statistically significant. This means that changes in T cells are improving. [25].

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Previous studies showed anemia prevalence ranging from 66% to 85% among people living with HIV [26]. Anemia can be caused by a defect in food intake, infectious or inflammatory intestinal malabsorption, or chronic bleeding whose cause is often a tumor (gastrointestinal Kaposi sarcoma). A vitamin B12 deficiency (by malnutrition, maldigestion, etc.) or folate deficiency could explain this anemia. It should be noted that the presence of light anemia is persistent despite taking ARVs; this persistent anemia is certainly linked to the fact that some ARV molecules, such as AZT, 3TC, and TDF (reverse transcriptase inhibitors), have myelossupressor effects; for example, AZT inhibits erythrocyte production [18, 27]. This effect is controlled by medical surveillance, which prevents the development of profound anemia.

Regarding the evolution of platelets, our study showed thrombopenia, suggesting that the decrease of platelets is one of the manifestations of HIV. In 2002, Youssefian et al. identified the virus in human platelets and megakaryocytes [28]. The low platelet count can be attributed to the interaction that occurs between the viruses, megacaryocytes, and platelets. More platelets and megacaryocytes have some receptors that promote the entrance of HIV-1; megacaryocytes express the CD4 receptors [29] and co-receptors like CCR3 and CXCR4 positive, which can be transformed into CXCR4 negative and promote the entrance of HIV [30] leading to compromised bone marrow production [31]. Platelets, on the other hand, do not express the CD4 molecule but express a receptor called dendritic cell-specific ICAM-grabbing non-integrin (DC-SIGN) [32], which has the ability to bind HIV-1, as well as co-receptors CXCR1, 2, 4, and CCR1, 3, 4, and 5 [33] to allow the entrance of the virus into platelets. Indeed, HIV-1 was found in the platelet secretion products [28], suggesting that platelets release the virus by exocytosis and can also pick it up by endocytosis. Thus, impaired thrombopoiesis (due to impairment of megakaryocytes by the virus) and platelet infection by virus lead to the immunological destruction of platelets by immunoglobulins (Ig) G [34] in relation to the reduction of their life expectancy and strengthening their sequestration by macrophages and spleen with inefficient compensation.

The consistent reduction of thrombocytopenia after the introduction of highly active ARV after two months of therapy is probably due to its ability to limit the damage caused by the uncontrolled replication of HIV and opportunistic infections. Since platelets play a role in antimicrobial control, they bind to infectious agents and neutralize them to form platelet aggregates [34]. Given the immune reactivation phenomenon that occurs in the first months of ARV therapy [27], most opportunistic infections are controlled; platelets are immediately free to circulate in the blood. As the

lymphocyte levels increase, antiretroviral treatment success should also be linked to a significant improvement in platelet count.

The main strength of this study is the fact that it was carried out in resource-limited settings in which the prevalence of HIV infection is high, and very few studies have been carried out after two months of ART therapy. A limitation of this study was that we did not measure the viral load.

5 Conclusion

The consistent reduction of thrombocytopenia after the introduction of highly active ARV after two months of therapy is probably due to its ability to limit thCD4 lymphopenia, monopenia and thrombocytopenia induced by HIV infection are corrected maximally during the first 2 months of ART and tend towards stable values over time, while moderate anemia remains persistent with antiretroviral therapy.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no competing interests.

Statement of ethical approval

Ethical clearance for this study was obtained from the Cameroon National Ethics Committee (N° 237/CNE/SE/2012). Standard procedures were used and involved minimal risk to the participants..

Statement of informed consent

Participation in this study was voluntary. A signed consent form was sought from all participants.

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Authors' contributions

- Elise Guiedem conceived and designed the study, implemented sample collection and laboratory analysis, and wrote the first draft of the manuscript.
- Céline Nkenfou participated in the design of the study and the writing of the article.
- Emilia Lyonga participated in the design of the study and substantially revised the first draft of the manuscript.
- Martha Masembe contributed to the laboratory analysis and made some corrections to the draft.
- Gregory Mwambo revised the first draft of the manuscript.
- George Mondinde Ikomey participated in the design, laboratory implementation, and supervision of the study.

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