



Some Markers of Chronic Immune Activation in Young Born HIV Positive Under Antiretroviral Treatment at the Yaounde University Teaching Hospital, Cameroon

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Abstract

Background: The clinical importance of the CD4:CD8 ratio in people living with HIV (PLHIV) on antiretrovirals (ARVs) is increasingly recognized. Indeed, the persistence of an inverted CD4:CD8 ratio under ARV was associated with a higher level of immune activation and a higher risk of occurrence of comorbidities classifying or not AIDS. However, due to events that have become rare, few studies report the prognostic value of the CD4:CD8 ratio in PLHIV born to HIV positive. **Objective:** The aim of the present study was to identify biomarkers of immunological activation involved in the monitoring of people born HIV.

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Methods: The study was longitudinal prospective carried out at the Yaounde University Hospital, from 2020 to 2021, on young people born HIV positive, aged over 19, on ARV, with an undetectable viral load, and whose medical file was available and complete within the Approved Treatment Center. Participants' socio-demographic and clinical data were recorded, and rapid diagnostic tests for infections with HBV (Hepatitis B Virus), HCV (Hepatitis C Virus), EBV (Epstein Barr-Virus), CMV (Cytomegalovirus) were carried out. Determination of the T lymphocyte profile was carried out by flow cytometry. Participants' parameters were taken at inclusion (P1) and 12 months later (P2). Statistical analysis was carried out with version 22.0 of the Statistical Package for Social Sciences (SPSS) software, chi-square and Spearman's correlation coefficient were calculated for comparison purposes.

Results: 74 participants were enrolled, with the sex-ratio of 0.45 and the age group of 5-10 years was the largest 33.78% (n=25), and children were the most affected at 56.76% (n=42). From P (1) to P (2) the most common therapeutic protocol was TDF/3TC/EFV with 86.96% (n=59) participants and 29.73% (n=43) participants. The prevalence of comorbidities of P (1) and P (2) was 43.24% and 50%. The average of CD4+ and CD8+ counts were respectively 536.76±21.63 cells/mm³ and 754.93±50.78 cells/mm³ at P (1) and 908.30±50.25 cells/mm³ and 1202.30 ±447.70 cells/mm³ at P (2). From P (1) to P (2), the average CD4:CD8

ratio was 0.72 and 0.93. At P (1), the most common liver virus was HBV 22.97% (n=17), at P (2) it was CMV 95.95%. The CD4+:CD8+ ratio <1 was found associated with high CD4+ values (p=0.001) and co-infection with CMV and HSV-1/-2 (p<0.001). **Conclusion:** An increase in CD4+ and CD8+ counts during the follow-up period was found associated with CD4:CD8 ratio <1, the CD4+:CD8+ ratio which also appeared to be influenced by CMV co-infection.

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Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

CMV: Cytomegalovirus

CSCCD: Center for the Study and Control of Communicable Diseases

EBV: Epstein-Barr Virus

FMBS: Faculty of Medicine and Biomedical Sciences

HIV: Human Immunodeficiency Virus

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

HTLV1/2: Human T Leukemia Virus 1 and 2

VL: Viral Load

Introduction

Since the Human Immunodeficiency Virus (HIV) discovery in 1983, the number of people living with HIV (PLHIVs) worldwide is still increasing and in 2020, it has been estimated at 37.6 million. In Central Africa, Cameroon is one of the most affected countries, with 3.1% of prevalence what makes HIV/AIDS, a real public health problem worldwide, affecting adults, adolescents and children of both sex [1,2]. Immune activation and inflammation are hallmarks of chronic untreated HIV disease and have been associated with a range of clinical endpoints and serious non-AIDS events (SNAEs) [3]. CD4+ T cells or lymphocytes (CD4+ LT) play a pivotal role in the regulation of the immune system, protecting the host against various pathogens and autoimmunity. These cells modulate the immune activation by orchestrating responses of B- cells, CD8+ T cells and other components of the immune system [4]. During chronic infections and cancer (which involve persistent antigen exposure), a chronic inflammation response is implemented leading to CD4+ T cells loss [5]. With the advent of triple

antiretroviral therapy (ART), the life prognosis of PLHIVs was improved by reducing viral load (VL) to its undetectability, while increasing the level of CD4+ T cells [6]. With the treatment generalization to all affected HIV people, regardless of the infection staging, a life expectancy was observed and VL becoming undetectable [7,8]. However, the occurrence of comorbidities not related to acquired immunodeficiency syndrome (AIDS) were still described [9]. Indeed, chronic immune activation persists even in HIV-infected patients in which viral replication is successfully inhibited by antiretroviral therapy, with the extent of this residual immune dysfunction associated to proportions of T-cell subsets (CD4+ and CD8+ T-cells), a marked decrease in CD4+ T cell numbers with significantly decreased mean CD4/CD8 ratios [10,11]. But is also characterized by the reactivation of viral infections Cytomegalovirus (CMV), Epstein Barr-Virus (EBV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human T Leukemia Virus 1 and 2 (HTLV1/2), taking drugs and antiretrovirals [12]. And a CD4:CD8 ratio which has already been associated in several studies with immune activation in people infected with HIV [13,14].

The CD4:CD8 ratio represents the number of CD4+ T cells divided by the number of CD8+ T cells in the same volume of total blood. It is obtained during the realization of a lymphocyte immunophenotyping, allowing fine analysis of characteristics of circulating lymphocytes in a patient. Even if no value is not consensual when analyzing the literature, the changes in this ratio therefore directly reflect the changes current rates of LT CD4+ and LT CD8+. The study of this ratio mainly concerned situations in which it was reversed (value less than 1), due to a decrease in the CD4+ T cells count and/or an increase in CD8+ T cell

counts. It seems that the inversion of this ratio is the marker of a chronic activation of the immune system [15]. In Cameroon, very little data is available regarding immune activation in young people born HIV-positive to HIV-positive mothers. For the present study, we hypothesized that PLHIV have higher T-cell immune activation and that immune activation would be more pronounced with increasing age, the stage of the disease and viral coinfections.

The aim of the present study was to identify the different biomarkers involved in chronic immune activation in people born HIV positive at the Yaoundé University Teaching Hospital in Cameroon.

Materials and Methods

Study Design and Setting

Study Population

A longitudinal prospective study was conducted at the Yaoundé University Teaching Hospital, on people born with HIV infection from July 2020 to October 2021. The choice of this hospital was motivated by the availability of a care unit for PLHIV with a large number of patients followed. Hence the probability of having the sampling required for our work.

Study population

The inclusion was progressive and each participant was enrolled for six months during the study period. We enrolled patients that met the inclusion criteria that were: age ≤ 19 years, a positive HIV test, treatment with ART, undetectable viral replication (<50 copies/mL), having an available and complete medical record within the service, and be available for the study 12 months later at least. A comprehensive questionnaire was performed at inclusion, in order to have clinical data. Completion data were obtained from medical records.

Sampling and Immunophenotyping:

For each patient, five milliliters of blood were drawn in heparin tubes (Becton Dickinson (BD), Franklin Lakes, NJ, United States) at the inclusion and 12 months later. The samples were coded and were transported to 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.

Torch Testing

The viral serology of HBV, HCV and CMV was done, at the Microbiology laboratory of the University of Yaounde I at the faculty of science, using the technique of immunochromatography on strip and cassette. For the purpose, the HBV 5 in 1 Combtest (S/P) Nantong, (Diagnose Biotechnological., China), the One Step Rapid Test HCV Ab Test Cassettes (S/P) (High-top Biotech, China) and The One Step IgM/IgG CMV (Bioneavan CO.LTD., Beijing) were used. Serology for the search for EBV virological status: was performed in (plasma) samples by a qualitative method using Epstein Barr (EB)-IgM antibody Rapid Diagnostic Tests, according to the kit manufacturer's instructions (Bi-oneavan co.LTD., Beijing

Immunophenotyping

The measurements of CD4+/CD3+ and CD8+/CD3+ T cells were done based on the principle of immunophenotyping. Fifty microliters (50 μ L) of whole blood were used for the analyzes using the BD FACS Count reagent kit, automated machine (BD Biosciences, San Jose, California, USA). Samples, including quality controls, were analyzed based on the manufacturers' guidelines [7].

Sample Size Calculation

The minimum sample size was 46.7 participants. The calculation of this Sample size was made using the prevalence of HIV, which are 3.1% in Cameroon [2]. We used the following formula [16]:

$$N = \frac{P(1 - P)(Z_{1-\alpha})^2}{i^2}$$

Variables Collected

For each participant, qualitative and quantitative variables were collected either by interview or blood samples analysis. The qualitative variables collected were: sex, drug consumption, alcohol consumption before illness; tobacco consumption; type of antiretroviral treatment, HCV-Ab; HBs-Ag, RV-Ab, To-Ab, HSV-1/-2 Ab, CMV-Ab, EBV-Ab, stage of the disease, type of HIV, comorbidities. The quantitative variables collected were age; CD4+ T cells count, CD8+ T cells count, CD4+:CD8+ ratio.

Statistical Analysis

The coded data was entered in Microsoft Excel 2016

and transferred to the Statistical Package for Social Sciences (SPSS) software version 22.0. Clinical characteristics are presented as median and mean or as proportions (%). There is no established upper limit of normal for T-cells subsets. The Spearman correlation and The Chi-square test was computed for comparing proportions between CD4:CD8 ratio, CD4+ T cells count, CD8+ T cells count and some clinical parameters. Any value of $p < 0.05$ was considered statistically significant for a 95% confidence interval.

Ethical Considerations

The study was approved by the Regional Ethics Committee for Research in Human Health (N°0082/CRERSHC/2023) and the Ethics Committee of the Yaoundé University Teaching Hospital (N°494/AR/CHUY/DG/DGA/CAPRC) Center before the start of the work. Written informed consent and verbal assent when appropriate was obtained from all participants/parents.

Results

Sociological and Demographic Characteristics

From July 2020 to October 2021, 74 young patients born with HIV were included in the present study. The participant's age ranged from 3 to 19 years, with a median age of 7 years old, the most representative age range was 5-10 years old (Fig 2), with a proportion of 33.78% (n=25). Our population was female predominant, 51 girls (68.92%) with a sex ratio of 0.45 (Fig 1). At the first sample (P1), among the 74 participants, it appears from this study that 24% consumed (n=18) other drugs, 31% took tobacco (n=23), out of 22.97% (n= 17) consumed alcohol. At the second sample (P2), 43.24% consumed (n=32) other drugs, 39.19% took tobacco (n=29), 36.49% (n=27) consumed alcohol (Fig 3)

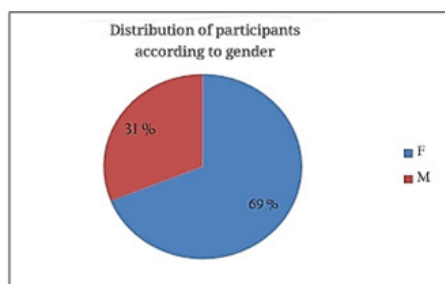


Figure 1: Distribution of Participants According to Gender

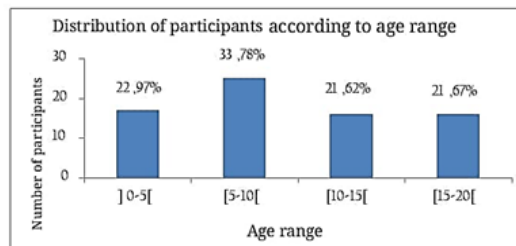


Figure 2: Distribution of Participants According to Age

Clinical Characteristics

Concerning clinical characteristics, 70 patients (94.59%) were in stage I according to the body weight loss criteria of the classification of WHO [9]. Clinical history of the disease discovery was after any consultation in majority (56.76%, n=42), then following a consultation for chronic fever at the first sampling (33.78%, n=25) and (31.08%, n=23) at the second sampling. At the first sampling, the most widely used therapeutic protocol was Tenofovir-Lamivudine-Efavirenz (TDF/3TC/EFV) with 59 patients (79.74%) and at the second sampling The most widely used therapeutic protocol was Tenofovir-Lamivudine-Efavirenz (TDF/3TC) /EFV) with 43 patients (58.11%), with a median treatment duration of 6 years (comprised between 2 and 18 years) (Fig 4). Some viral opportunistic infections (EBV, CMV, HBV and HCV infections) were detected at the first sampling, in 24 participants (32.43%) and the one to EBV was high (22.97, n=17), and at the second sample in 30 participants (42.86%) and the one from CMV was high (95.95%, n=71). These participant's characteristics are shown in Table 1.

Table 1: Distribution of Participants According to IgG/IgM Antibodies against HCV-Ab, HBs-Ag, CMV, and IgM against EBV Results

Infectious agent	First sampling		Second sampling	
	N (%)	IC95%	N (%)	IC95%
HVC	7(9.46)	[3.9-18]	7(9,46)	[3.9-18.5]
HVB	14(18.9)	[10.8-29]	14(18.9)	[10.75-29.7]
CMV	9(12.2)	[5,6-23]	71(95.95)	[88.6-99.2]
EBV	17(22.97)	[13.9-34.2]	17(23)	[14-34]

T-lymphocyte Measurements

For the first measurements, the means of CD4+ and CD8+ cells count were respectively 536.76 ± 21.63 cells/mm³ and 754.93 ± 50.78 cells/mm³, and for the second 908.30 ± 50.25 cells/mm³ and 1202.30 ± 447.70 cells/mm³. The mean of the CD4:CD8 ratio was 0.72 at the inclusion and 0.93 twelve months later. The follow-up period was around 12 months and the mean CD4:CD8 ratio increased during this period from 0.72 to 0.93. Regarding lymphocytes, there was an increase in CD4+ and CD8+ cells count (Table 2). Regardless of the study period, the majority of patients remained with CD4:CD8 ratio <1 (89.02% at the inclusion and 87.8% 12 months later) (Table 3).

Comparisons Between CD:CD8 Ratio and Other Patient Characteristics

Having a CD4:CD8 ratio <1 was associated with elevated proportions of CD4+ T-cell subsets ($p=0.001$), stage I disease ($p<0.001$) and viral co-infections ($p<0.001$) $p<0.001$), more with a positive CMV IgG. There was not significantly association with ARV protocols (Table 4).

Table 2: Distribution of CD4:CD8 ratio parameters in the population

Variables (cells/mm ³)	First sampling		Second sampling	
	CD4:CD8 ratio	N (%)	CD4:CD8 ratio	N (%)
LT CD4+	< 1 (0,85)	66 (89,02)	< 1 (0,9)	65 (87,8)
LT CD8+				
LT CD4+	≥ 1 (1,16)	8 (10,08)	≥ 1 (1,01)	9 (12,2)
LT CD8+				

Table 3: Correlations Between CD4:CD8 ratio < 1 and Other Patient Characteristics (First sam-pling)

Patients' characteristics		First sampling (n=66,89,02%)	
(n=74)	n (%)	r (95% CI)	P Value
CD4+ (cells/mm3)	600 (n=66, 89.02 %)	1.24 (1.2 to 1.3)	0.001
Stage of the disease	Stage I (n=62,83.78%)	4.2 (3.2 to 7.3)	<0.001
ARV protocol	AZT/3TC/NVP (n=1, 1.35%)	0	0.821
	TDF/3TC/EFV (n=58,74.32%)	-1.10 (61.39 to -0.88)	<0.001
	TDF/3TC/ATV (n=5, 6.75%)	0	0.321
Viral opportunistic in-fec-tion	HBV (n=14,18.92%)	0.4 (76.8-100)	<0.001
	CMV (n=9, 12.16%)	0.5 (66.3-100)	<0.001
	HCV (n=6 ,8.1%)	-0.11(-0.54 to 0.19)	<0.001
	EBV (n=13, 17.57%)	0.4 (76.8-100)	0.04
	HSV-1/-2 (n=69, 93%)	1 (0.99 to 1.02)	<0.001

Table 3: Correlations Between CD4:CD8 ratio < 1 and Other Patient Characteristics (Second sam-pling)

Patients' charact-eris-tics (n=74)	Second sampling (n=65, 87,8%)		
	n (%)	r (95% CI)	P value
CD4+ (cells/mm3)	846.50 ± 49.71 (n=65, 87%)	1.54 (1.32 to 1.63)	0.001
Stage of the disease	Stage I (n=61,82.43%)	4.2 (3.2 to 7.3)	<0.001
ARV protocol	TDF/3TC/D (n=17, 6.75%)	0	0.821
	TDF/3TC/EFV (n=43,74.32%)	-1.10 (61.39 to -0.88)	<0.001
	TDF/3TC/LPV (=5, 6.75%)	0	0.321
Viral oppor-tunistic infec-tion	HBV (n=14, 8.92%)	0.4 (0.6 to 0.34)	<0.001
	CMV (n=71, 95.95%)	1.02 (1.01 to 1.04)	<0.001
	HCV (n=6, 8.1%)	-0.11 (-0.54 to 0.19)	<0.001
	EBV (n=13,17.57%)	0.4 (76.84-100)	0.04
	HSV-1/-2 (n=69, 93%)	1 (0.99 to 1.02)	<0.001

Table 4: Correlations between CD4:CD8 ratio < 1 and other patient characteristics (Second sam-pling)

Patients' characteris-tics (n=74)	Second sampling (n=65, 87,8%)		
	n (%)	r (95% CI)	P value
CD4+ (cells/mm3)	846.50 ± 49.71 (n=65, 87%)	1.54 (1.32 to 1.63)	0.001
Stage of the disease	Stage I (n=61,82.43%)	4.2 (3.2 to 7.3)	<0.001
ARV protocol	TDF/3TC/D (n=17, 6.75%)	0	0.821
	TDF/3TC/EFV (n=43,74.32%)	-1.10	<0.001
	(n=43,74.32%)	(61.39 to -0.88)	
	TDF/3TC/LPV (=5, 6.75%)	0	0.321
Viral oppor-tunistic infec-tion	HBV (n=14, 8.92%)	0.4 (0.6 to 0.34)	<0.001

	CMV (n=71, 95.95%)	1.02 (1.01 to 1.04)	<0.001
	HCV (n=6, 8.1%)	-0.11 (-0.54 to 0.19)	-0.11 (-0.54 to 0.19) <0.001
	EBV (n=13,17.57%)	0.4 (76.84-100)	0.4 (76.84-100) 0.04
	HSV-1/-2 (n=69, 93%)	1 (0.99 to 1.02)	<0.001

Discussion

In this study we included a cohort of well-treated young patients born with HIV with undetectable viral replication. We found an increase in the mean level for both CD4+ and CD8+ cells during the follow-up period, an average of, respectively, 536.76 ± 21.63 cells/mm³ and 754.93 ± 50.78 cells/mm³ for the first measurement and 846.50 ± 49.71 cells/mm³ and 1202.30 ± 447.70 cells/mm³ for the second. We observe a phenomenon of immune reconstitution with increase of LT CD4 and the reconstitution over time of CD8+ cells explaining the value less than 1 in the ratio, but still high. A recent study found that CD4+ and CD8+ cell count trajectories reached above the median reference value. Elevated CD8+ cell count levels are suggestive of ongoing residual immune activation, and residual HIV viremia, coinfections (such as CMV), microbial translocation, loss of immune regulatory responses, and hypercoagulability are all thought to contribute [18]. Another team conducted a study on the impact of age and HIV status on immune activation, senescence and apoptosis. Their results support that well treated PLWHIV have residual immune dysfunctions such as elevated proportions of CD8+ cell count and immune activation [10]. In this study, we have established a longitudinal evolution of the ratios as for absolute values of CD4+ and CD8+ T lymphocytes. Then we can notice that the presence of an inverted CD4/CD8 ratio indicates an active lymphocytosis, which is observed in the vast majority of study participants (89.02% for the count 1 and 87.8% for the count 2). In literature, an inverted CD4:CD8 ratio has been associated with altered T-cell subsets, and it often remains inverted due to persistent high CD8+ T-cell count even in persons with early treatment start [19]. There may be an association between the CD4:CD8 ratio and immune activation in patients

with suppressed viral load. During HIV infection the ratio struggles to normalize [18]. The CD4:CD8 ratio necessarily remained inverted, which reflects immune activation. After one year of follow-up, the CD4:CD8 ratio ≥ 1 concerned participant with 16 years of undetectability. A cross-sectional study carried out in a cohort in England showed that almost 66% of participants presented a normalized CD4+:CD8+ ratio among children and adolescents with undetectability for almost 11 years of follow-up [20]. Studies have shown that the immune risk profile depends on the inverted CD4:CD8 ratio with a lower level of LTCD4+ and an increased level of LT CD8+ [21].

The CD4:CD8 ratio <1 was statistically associated with elevated proportion of CD4+ ($p=0.001$). We found no major difference in association with viral coinfections ($p<0.001$) apart from a predominance of CMV infection. The appearance of viral co-infection is a sign of the disease progression; however, it was observed that the majority of participants were in an early stage of the disease. CMV infection may contribute to CD8+ T-cell expansion and subsequently an inverted CD4:CD8 ratio, but Hove-Skovsgaard et al. investigated that the impact of CMV coinfection on T-cell residual immune dysfunction in persons living with HIV has been debated. Recently, CMV-specific T cell responses, but not CMV IgG level, has been associated with CD8+ cells count immune activation and senescence [10].

In the current study, participants were found to have high levels of anti-CMV antibodies. Indeed, studies have highlighted the idea that CMV infection is one of the causes associated with the aging process, with recurrent or chronic coinfections with other pathogens. A recent study demonstrated that in the early stages

of HIV infection, an inflammatory environment is created which aggravates the destruction of CD4+ T cells and the immune deficiency with respect to chronic viral infections frequently associated with HIV infection causing loss of control and reactivation of HBV or HCV, CMV or EBV. These viral infections themselves activate both innate defenses and immune responses specific to these agents, further amplifying the chronic immune activation caused by HIV itself, creating for years in the absence of treatment, a vicious circle of inflammation/immune exhaustion/viral reactivation and the increase in cancers is observed at the same age compared to the general population and concerns both virus-induced cancers (linked to EBV, HBV, HCV or HPV) and non-oncovirus-induced cancers [22]. Taking antiretrovirals, lack of lymphopenia, undetectable viral load, presence of viral coinfections while the cohort is at an early stage of HIV infection, the persistence of an inverted ratio suggested that all these factors are independent of HIV presence, and indicative of chronic activation of the immune system.

HSV infection was determined with HSV-1 or HSV-2. The presence of circulating HSV1-IgG is an indication of the potential risk of recurrent infection. Since during an HSV1 infection the infected person remains a source of contamination all his life, therefore is a carrier of the virus. Its presence in patients with HIV justifies the endemic characteristics of sub-Saharan Africa [23].

EBV and CMV co-infections appear to be more frequent in the literature. A possible explanation is that most of the patients in this cohort, although hospitalized, were seen in outpatient care [24]. Testing for the presence of CMV infection in HIV-positive patients is particularly important in assessing disease severity and monitoring response to treatment. The influence of factors not investigated in this study such as genetics, nutritional status, socio-economic conditions could explain these a priori weight results concerning the prevalence of CMV [25]. Indeed, both HIV and CMV are associated with increased immune activation and inflammation related morbidities, including neurocognitive impairment, cancer, and cardiovascular disease [26-30]. Because almost all HIV-infected individuals are coinfecting with CMV, it is hard to distinguish between HIV, CMV, and combined effects

on inflammation and disease progression [31].

As strengths of our study, the demonstration of the presence of Herpesviridae in young people born HIV positive to HIV positive mothers, of certain immune activation parameters, the demonstration of comorbidities and sociological parameters such as the use of drugs and tobacco.

As limitations of our study, the inclusion of a small number of patients, which does not allow robust statistical analysis, the monocentric nature of the study, the fact that large variations in ratio values could be detected if the time interval between readings was high, absence of use of genomic techniques to better characterize microbes, the low number of activation markers used in this work.

Conclusions

Our study had demonstrated that despite taking ARV, and no HIV viral load, viral co-infections appear, and an inverted CD4:CD8 ratio remains, because of persisting high CD8+ cells counts. Further investigations concerning the role of CD8+ cells during an HIV-1 infection, which could reveal more details about HIV-1 disease progression. It is therefore important to analyze the evolution of the CD4:CD8 ratio kinetics, and the increase in follow-up time and the repetition of the measurements allows a better appreciation of the evolution of the CD8+ cells and therefore of the value of the ratio. The use of the CD4:CD8 ratio therefore seems an interesting marker to use in clinical practice, because of its easy application and simplicity of interpretation. These data indicated a high exposure of these viruses in childhood, but also reactivations for CMV (presence of IgM), and we had allowed to conclude an association between CMV, HVC, HBV and CD4:CD8 ratio.

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Author Contributions

Mbongue-Mikangue. C. André. conceptualized the research, designed the proposal, developed the questionnaire and prepared the manuscript for publication. Mbongue-Mikangue. C. André helped conceptualize the research and revised the earlier drafts and corrected them before preparing a final report. They were also involved with the other authors in data collection and analysis. Author provided critical analysis to the earlier drafts of manuscript and read the final version of manuscript for publication in a scientific journal.

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Conflicts of Interest

The authors declare no conflicts of interest.

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