Early Effects of Antiretroviral Therapy on Vitamin D Status and Some Nutritional Markers of HIV-1 Infected Patients: A Case Control Study in a Sub-Saharan Africa Setting

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Abstract:

Objective: *To evaluate the early effect of antiretroviral therapy (ART) on vitamin D status and nutritional markers in HIV-1 infected patients.*

Results: *We compare the vitamin D status, and serum level of calcium, phosphorus and ferritin of 40 consenting HIV-1 positive patients at one month of ART with 40 ART-naïve HIV patients, as a control group. There was no statistical difference in vitamin D, phosphorus, calcium and ferritin concentrations between groups. Albuminemia was higher in patients on ART (36.1 [29.7-40.1]) compare to ART-naïve patients (33.7 [27.5-36.7]) (p<0.05).At one month of ART, we observed an increase in albuminemia, while vitamin D, phosphorus, calcemia and ferritinemia remain unchanged..*

Keywords: *Albuminemia, Antiretroviral Therapy, Calcemia, HIV-1, Phosphorus, Vitamin D*

Abréviations: *ART: Antiretroviral Therapy, HIV: Human Immunodeficiency Virus;*

1. INTRODUCTION

By the end of the year 2018, United Nations for AIDS estimates that 37.9 million people were living with AIDS worldwide. Africa is the most affected continent with 25.8 million people infected, and around 540 thousand deaths out of the global 770,000deaths in 2018 [1]. HIV infection cause a drop in immunity, chronic inflammation and oxidative stress wichpredisposes to opportunistic infections such as tuberculosis, metabolic complications and carcinogenesis, thus worsening the prognosis of the disease [2,3].Two third of HIV patients livein LMIC (Low and Middle Income Countries) and face difficulties in accessing care. Also they suffer from undernourishment and malnutrition, and its resulting nutritional deficiencies [4].

Malnutrition in Africa accounts for about a quarter of the worldlwide prevalence. Climatic changes, conflicts and economic instability increase the burden of food insecurity and malnutrition in Africa [5]. HIV and malnutrition have bidirectional interactions; HIV contributes to malnutrition by reduced nutrient intake, malabsorption, increased energy expenditure and endocrine dysfunction [6,7]; On the other hand, malnutrition in HIV patients increases the risk for opportunistic infections, and reduces the effectiveness of antiretroviral treatment leading to a high mortality [7,8]. Malnutrition and undernourishment include various deficiencies such as vitamin D deficit, which prevalence varies between 18 and 46% in Africa [9]. Vitamin D deficit is particularly harmful in HIV-infected patients because its plays an important role in innate and adaptive immune response, inflammation, oxidative stress and endothelial dysfunction [10,11]. It's deficiency in HIV infected patients will worsen the already decreased lymphocyte count, increasing morbimortality [11].

Antiretroviral therapy (ART)reduces viral replication, increase CD4 counts and progressively restores the immune and nutritional status. However, few data have reported its effects on vitamin D status in

the early months of treatment. We conducted this study to assess the effects of ART on nutritional and vitamin D status in people suffering infected with HIV-1 after the first month of treatment.

2. MATERIAL AND METHODS

2.1. Study Framework

We conducted cross sectional study from January to April 2019 in the HIV unit of the Yaoundé Central Hospital.

2.2. Participants

Participants were 80 consenting HIV-1 positive patients aged 18 years and above. They were equally divided into two groups: Group 1 made up of 40 patients receiving ART (Tenofovir/ Lamivudine/ Efavirenz) at the first month of treatment, and a good adherence to treatment; Group 2 made up of 40 patients newly diagnosed on ART-naïve. The sample size was estimated using Cochran (1965:75) formula with 80% power and 5% error. The sampling was consecutive and non-exhaustive.

2.3. Ethical Considerations

The study was approved by the Institutional Ethics Committee of the Health Sciences School of the Catholic University

2.4. Data Collection

For each participant, we reported the age, gender and biological analysis were performed using 10mL of peripheral venous blood sample to assess serum concentrations of calcium, albumin, phosphorus, ferritin and vitamin D. Albumin, calcium and phosphorus were determine using colorimetric techniques. Ferritin and vitamin D were determined using the competitive-ELISA technique. Calcemia was corrected with albumin.

2.5. Operational Terms

Vitamin D deficiency was defined less than 20 ng/mL. It was severe, moderate and mild respectively less than 5ng/mL, between 5 and 9 ng/mL and between 10 and 19 ng/mL. Normal vitamin D level could be low (between 20 and 29 ng/mL), or high (above 30 ng/mL). Hypoalbuminemia was defined for a value less than 34g/L; Hypocalcemia was defined for a corrected calcemia less than 80mg/L. Hypoferritinemia was considered <30ng/mL and <10ng/mL respectively for men and women. Phosphorus levels was considered low for a value less than 26mg/L (hypophosphatemia).

2.6. Statistical Analysis

Data were analyzed using the software SPSS version 22.0. The data were reported in median and interquartile range (25th and 75th quartiles) for quantitative variables and in effectives with proportions for categorical variables. We used the Fisher's exact test to compare proportions, and Median test for median comparison. The threshold of significance was set at 0.05.

3. RESULTS AND DISCUSSION

3.1. Results

Two third of the sample were female with no statistical difference between groups ($p \geq 0.05$). The median age was 43 [34-49]years for group 1 participants, but the difference was not statistically significant with group 2.

Vitamin D level comparison revealed no statistically significance difference between both groups ($p \geq 0.05$). Majority of the participants from both groups (40% and 37.5%) had a mild deficiency in vitamin D level. However, repartition of vitamin D status was quite similar in both groups. Hypophosphatemia was observed in 15%, and hypocalcemia in 50% of ART naïve patients. However, there was no difference in phosphorus and calcium metabolism in both groups

Regarding ferritin, serum concentration ofparticipants in group 1 was lower (11.8 [8.6-13.1] ng/ml) compared to group 2 patients (13.2 [9.6-13.8] ng/ml) with no statistical difference ($p \geq 0.05$).

Concerning nutritional status, albuminemia was higher in patients from group 1 (36.1 [29.7-40.1]) than in ART naïve patients (33.7 [27.5-36.7]) ($p < 0.05$).The prevalence of hypoalbuminemia was lower in group 1(35%) than group 2 (52%). All the data are summarized in Table I.

Table1. *Clinical and biological characteristics of the study sample*

Variables	Group 1 (n=40)	Group 2 (n=40)	p value
Age, years	43,5 [34-49]	42.5 [33.3-46.8]	≥0.05
Female, n (%)	31 (77.5)	26 (65.0)	≥0.05
Vitamin D (ng/mL)	21.21 [12.68 - 32.72]	21.10 [16.33 - 35.52]	≥0.05
Moderate deficiency; n (%)	3 (7.5)	2 (5.0)	
Mild insufficiency; n (%)	16 (40.0)	15(37.5)	
Normal low; n (%)	10 (25)	9 (22.5)	
Normal high; n (%)	11 (27.5)	14(35)	
Calcemia, (mg/L)	83 [78.74 - 90.95]	86.24 [76.25 - 100.75]	≥0.05
Hypocalcemia; n (%)	24 (60)	20 (50)	
Ferritinemia (ng/mL)	11.80 [8.62-13.17]	13,20 [9.65-13.80]	≥0.05
Hypoferritinemia; n (%)	21 (52.5)	24 (60.0)	
Albuminemia (g/L)	36.15 [29.77-40.10]	33.75 [27.50-36.72]	**<0.05**
Hypoalbuminemia n (%)	14 (35)	21(52.5)	
Phosphoremia (mg/L)	37.15 [29.02 - 44.82]	36.50 [28.75 - 40.30]	≥0.05
Hypophosphoremia, n (%)	7 (17.5)	6 (15.0)	

3.2. Discussion

HIV is still a major public health problem especially in Africa. It is closely associated to various nutritional deficiencies which are hoped to be restored with ART. We conducted a cross sectional study to compare the vitamin D status and nutritional markers of HIV-1 patients on ARTwith ART naïve patients. It appears that albumin concentrations are higher in ART group, but all the other parameters were similar in both groups. Albuminemia is a marker of nutritional status and is correlated with HIV infection progression and mortality [12]. In this study, serum albumin concentration is higher in ART patients, which suggests a better nutritional status compared to naive ART patients. These results corroborate those found by Michael Carter where, in HIV patients, an average serum albumin level of 32 mg / L was found before the beginning of anti-HIV treatment and this increased significantly to 37.7 mg / L (p = 0.004) after treatment [13].Similar results was also found in a cohort study in Uganda with an improvement of the nutritional status after 3 years of ART [14]. HIV infection is associated with inadequate nutrient intake with anorexia, malabsorption and psychosocialissues[15,16]. Also, there is an increase in global metabolism in uncontrolled HIV infection, opportunistic infections and cytokines dysregulation which contributes to a poor nutritional status [17]. Therefore, antiretroviral therapy will reduce viral load and improve nutritional status in HIV patients.

Vitamin D has wide-ranging effects on the immune system and low serum levels are associated with worse clinical outcome. Its levels were similar in our study between ART patients and ART naïve patients. These results contrast some recent studies that suggest that antiretrovirals, particularly Efavirenz are associated with low serum concentrations. Carolien et al in 2008 in Netherland found that non-nucleoside reverse transcriptase inhibitor (NNRTI) were associated with vitamin D deficiency [18]. Nylen et al found in an Ethiopian cohort that Efavirenz based therapy is associated with high incidence of severe vitamin D deficiency [19]. These data suggest that ART in particular Efavirenz may leads to low levels of vitamin D. This effect of the Efavirenz is hypothesized to occur through the induction of 24-hydroxylase, a cytochrome P450 enzyme, that inactivates 25OH vitamin D and 1,25OH vitamin D[20]. Our findings, which differ from those found in the literature, can be explained by the duration of ART use. Indeed, in our study, the patients had been under treatment for less than 3 months. The results of Fiona et al. support this hypothesis because they found a sharp drop of serum concentration of vitamin D in the 6 first months after ART initiation, with a much slower decline or a stagnation between 24 and 48 weeks of treatment[21]. The effect of Efavirenz on vitamin D levels would therefore be more pronounced at the initiation of treatment and less pronounced over the long term.

The short duration of ART may also explain no difference in calcemia, phosphorus and ferritinemia in both groups which differs from the results of Noe et al, where they found an association between Tenofovir and high risk of hypocalcemia[22]. Hypocalcemia in ART patients can be explain by the effect of some antiretroviral therapies such as Tenofovir of Efavirenz on vitamin D metabolism, leading to low vitamin D concentration and therefore low calcemia[20,23]. Apart from ART duration, our population age was higher than those of the authors cited above. Contreras-Manzano et al found an increase in iron deficiency with age which is explained by reduce absorption and storage capacity due to age [24].

4. CONCLUSION

Our results suggest that early effects of ART at one month, on nutritional status is marked by an increase in albuminemia, while vitamin D, phosphorus, calcemia and ferritinemia globally remain unchanged. A follow up of this population will give further results.

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