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Vitamin D Deficiency and Evaluation of the Parathyroid Hormone Status in People Living with HIV in Côte d'Ivoire

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AJAA and LB wrote the protocol and the first draft of the manuscript. Authors KLS, MJMA and KDY supervised blood samples collection and managed the analyses of the study. Author AFY corrected the first draft of the manuscript. Author AJD designed the study, managed the literature searches and the final correction of the manuscript. All authors read and approved the final version of the manuscript.

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ABSTRACT

Background: Micronutrients play an important role in the human immune system. During HIV infection, the virus utilises the micronutrients of the body, for its replication causing metabolic disorders including phosphocalcic. Parathyroid hormone (PTH), vitamin D_3 (25-hydroxyvitamin D_3) and calcitonin are essential for the maintenance of phosphocalcic homeostasis and the proper functioning of the body. In Côte d'Ivoire, very few studies on HIV infection and the mechanism of phosphocalcic metabolism have been done. The purpose of this study was to determine the status of 25 (OH) D_3 and parathyroid hormone in people living with HIV.

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Methodology: The study involved 326 adults (163 HIV-positive and 163 HIV-negative as control subjects). After confirmation by HIV serologic scanning result, CD4 count was performed by flow cytometry (Facs Calibur). Assays for 25 (OH) D_3 and PTH were performed by HPLC and COBAS 6000 automated systems, respectively.
Results: A decrease in mean values of 25 (OH) D_3 (16 ± 0.46 ng / mL) was observed in 50% of HIV-infected on ART and 87% of these patients presented a normal PTH level (28 ± 1.95 pg / mL). Deficiency of 25 (OH) D_3 (20 ± 1.03 ng / mL) is higher in HIV-infected on ART who have a CD4 count < 200 cells / mL.
Conclusion: Parathyroid hormone levels were normal in this study. Insufficiency or deficiency of 25-hydroxyvitamin D_3 is more common in HIV-infected on ART with a CD4 count < 200 cells / mL. This decrease characterized the degree of immunodepression.

Keywords: 25-hydroxyvitamin D_3; ART; Côte d'Ivoire; HIV; parathyroid hormone.

ABBREVIATIONS

PTH : Parathyroid hormone
CYP27B1 : Cytochrome 27 B1
cART : Combined antiretroviral therapy
EDTA : Ethylene diamine tetra acetic
PLHIV : People living with HIV
FGF-23 : Fibroblast Growth Factor 23
VDR : Vitamin D Receptor
cAMP : Cyclic Adenosine monophosphate

1. INTRODUCTION

Human immunodeficiency virus (HIV) infection is pandemic affecting 33.3 million people worldwide. In 2015, 1.1 million deaths and 2.1 million new HIV infections were recorded [1]. Sub-Saharan Africa remains severely affected by this pandemic and accounted for about 70% of new HIV infections [2]. In Côte d'Ivoire, the prevalence rate reduced from 3.4% in 2012 to 2.7% in 2016 [3].

During HIV infection, the virus uses nutrients, including micronutrients of the body, for replication [4]. This causes disorders of mineral metabolism, including phosphocalcic [5,6]. The regulation of calcium and phosphorus homeostasis involves parathyroid hormone (PTH), vitamin D_3 (25-hydroxyvitamin D_3) and calcitonin [7]. PTH is secreted in the parathyroid glands. It is a hypercalcemic hormone. In case of hypocalcaemia, parathyroid hormon facilitates mobilization of bone calcium, stimulates the activation of vitamin D_3 in the kidneys, which in turn increases, the intestinal absorption of calcium, while inhibiting its excretion in the urine [8]. Vitamin D_3 is a circulating steroid hormone that exists in the human body in two forms: 25 (OH) D_3, a form of reserve that under the action of 1-α-hydroxylase or CYP27B1 renal, hydroxylated to 1,25-dihydroxyvitamin D_3 (1,25 $(OH)_2D_3$), its active form [9]. Its main role is the regulation of calcium and phosphate homeostasis [10]. It also controls cell proliferation and differentiation [11].

Concerning HIV treatment, combined antiretroviral therapy (cART) does not eradicate HIV, which persists for years and can re-establish replication if treatment is stopped [12]. cART expose HIV-infected patients to chronic adverse effects, including neurocognitive disorders, cardiovascular and metabolic diseases, kidney and bone diseases (osteopenia / osteoporosis) and cancer [13].

In Côte d'Ivoire, few studies about the mechanism of regulation of phosphocalcic homeostasis in HIV-positive Ivorian patients have been undertaken [6]. The main objective of this study was therefore to determine the 25-hydroxyvitamin D_3 and parathyroid status of HIV-positive patients.

2. MATERIALS AND METHODS

2.1 Type of Study

This is a cross-sectional descriptive study conducted from November 2015 to December 2016 at the Department of Fundamental Biochemistry and Medical at Institut Pasteur of Côte d'Ivoire (IPCI).

2.2 Biological and Technical Material

A collection of fasting venous blood samples from 326 adult subjects (163 HIV-positive patients and 163 HIV-negative controls) was obtained for the various biochemical and serological tests. HIV-positive pregnant women

were not included in this study. Thus, a blood tube containing EDTA (Thermo, Tokyo, Japan) was used for the determination of CD4 + T cell count (whole blood) of HIV-positive subjects. A blood tube without anticoagulant (dry tubes) was used for HIV serological tests and biochemical parameters. Finally, the blood glucose assay was performed in serum from tube containing potassium oxalate and sodium fluoride.

Two rapid serological tests were performed for the detection of anti-HIV antibodies: the Alere Determine™ HIV-1/2 immunochromatographic kit whose principle is based on the formation of an antigen-antibody complex revealed after staining [14] and the *SD Bioline* HIV-1/2 3.0 immunoenzymatic confirmation test based on the detection of anti-HIV1 and anti-HIV2 antibodies specifically directed against antigens [15].

2.3 Biochemical Parameters

The CD4 + T lymphocyte count was performed in flow cytometry on the Facs Calibur from whole blood collected in EDTA [16]. The assay of 25-hydroxyvitamin D_3 is carried out using UV detection in high performance liquid chromatography (HPLC) with a Waters® device, after extraction of soluble vitamins with hexane in the dark protected from the light according to the method described by Zaman et al. [17]. The parathyroid hormone assay, based on electro-chemiluminescence detection, was performed on COBAS 6000 [18]. Assay of biochemical parameters such as Creatinine, Urea, Blood glucose, Alanine aminotransferase, Calcium, Phosphorus, Magnesium and Alkaline phosphatase was performed on COBAS C311 HITACHI. The principle is based on enzymatic and colorimetric methods that use a chromogen. The intensity of the observed coloration is directly proportional to the concentration of the substance assayed [19].

2.4 Statistical Analyses

The statistical analyses were performed using the Graphpad Prism Demo 5 software. The ANOVA test, followed by the Turkey test, were used to calculate and compare the averages. The degree of significance has been set at 5%.

2.5 Ethical Considerations

The study was conducted in accordance with the Helsinki 2000 Declaration on HIV and AIDS Research in Poor Countries and in accordance with local legislation on the National Program for the Care of People Living with HIV / AIDS (Decree No. 411 of 23 December 2001). Furthermore, for the research, consent was obtained from individuals for the use of their blood samples collected during biological monitoring.

3. RESULTS AND DISCUSSION

3.1 Characteristics of the Study Population

The average age of the study population is 39 years for treated people living with HIV (PLHIV) and 32 years for untreated PLHIV with extremes of 18 to 49 years. The mean age of the control was 31 years with extremes of 18 to 49 years (Table 1).

3.2 Biochemical Profile of the Study Population

Among the biochemical parameters analysed (Calcium, Phosphorus, Magnesium, Alkaline Phosphatases, Alanine aminotransferase, Glycemia, Creatinine, Urea), only phosphorus was significantly higher in treated PLHIV (2.55 ± 0.37, $P< 0.0001$) and in untreated PLHIV (1.97 ± 0.25, $P< 0.0001$) than in controls (1.19 ± 0.03). The other values were in the range of the reference values (Table 1).

3.3 Vitamin D and Parathyroid Status of the Study Population

In this study, a deficiency (< 20 ng/mL) of 25-hydroxyvitamin D_3 was observed in 12% (19/163) of HIV-negative controls, 50% (60/120) in PLHIV on ART and 12% (5/43) in PLHIV without ART. Similarly, insufficiency (20-30 ng/mL) of 25-hydroxyvitamin D_3 was noted in 44% (72/163) of the controls, 33% (40/120) of the PLHIV under ART and 42% (18/43) PLHIV without ART. Finally, normal mean values (≥ 30 ng / mL) of 25-OH vitamin D_3 were obtained in 44% (72/163) of controls, 17% (20/120) of PLHIV on ART and 46% (20/43) PLHIV without ART (Table 2). Regarding PTH level, only 10% (12/120) of PLHIV on ART experienced hypoparathyroidism (<10 pg/mL). Table 2 also shows a normal level (10-65 pg/mL) of PTH in 96% (157/163) of HIV-negative controls and in almost all PLHIV without ART (100%, 43/43). Hyperparathyroidism was observed in 4% (6/163) of HIV-negative controls compared to 3% (4/120) of PLHIV on ART.

3.4 Vitamin D and Parathyroid Status According to CD4 T cell Level

In patients without ART, a decrease in mean values of 25-OH vitamin D_3 according to the degree of immunodepression was observed. However, in patients on triple therapy, mean 25-OH vitamin D_3 concentrations are within the normal range for CD4 + T cell count greater than 500 cells/mL (32 ± 2.41 ng/mL) and those between 349 - 200 cells / mL (31 ± 2.29 ng/mL). However, a 25-hydroxyvitamin D_3 deficiency was found in CD4 + T cell count between 499 - 350 cells / mL (23 ± 1.14 ng/mL) and below 200 cells / mL (20 ± 1.03 ng/mL) (Fig. 1a). As for parathyroid hormone, mean concentrations are normal for all CD4 + T cell count and the presence or absence of ART (Fig. 1b).

3.5 Vitamin D and Parathyroid Status According to Age

In the 18-25 age group, untreated patients have a normal 25 (OH) D_3 concentrations (27 ± 0.56 ng/mL) but high when compared to controls and treated patients (16 ± 0.66 ng/mL). However, the control populations have 25 (OH) D_3 insufficiency, whereas the treated patients have deficiency in 25 (OH) D_3 (Fig. 2a). For parathyroid hormone, concentrations were normal but slightly higher in treated patients (20 ± 1.47 pg/mL) than in controls (19 ± 1.02 pg/mL) and in patients without treatment (16 ± 0.73 pg/mL) (Fig. 2b).

In the 26-34 age group, treated patients and untreated patients showed 25 (OH) D_3 deficiency respectively (29 ± 2.98 ng/mL; 26 ± 0.67 ng/mL) compared to controls (31 ± 1.05 ng/mL) (Fig. 2a). In contrast, concentrations of PTH were lower (7 ± 0.56 pg/mL) in treated patients than in controls (26 ± 2.28 pg/mL) but normal in untreated patients (30 ± 2.27 pg/mL) (Fig. 2b).

In the 35-49 age group, 25 (OH) D_3 deficiency was observed in treated patients (24 ± 1.84 ng/mL) compared to controls (31 ± 1.99 ng/mL). 25 (OH) D_3 levels were normal in untreated patients (34 ± 2.42 ng/mL) (Fig. 2a). PTH mean values in controls (29 ± 3.35 pg/mL), treated patients (28 ± 2.39 pg/mL) and untreated patients (28 ± 2.45 pg/mL), were in the range of normal reference values (Fig. 2b).

4. DISCUSSION

In this study, the average ages are 38 years for treated PLHIV and 31 years for untreated PLHIV. The population affected by HIV infection is young, more sexually active and economically active [20]. In Spain, an average age of 37 years has been reported [21]. A similar study conducted with a population aged 18 to 60 found an average age of 36 years [22].

The primary function of 25 (OH) D is the regulation of calcium and phosphate homeostasis [10]. In this our study, calcium levels are normal, however we observed hyperphosphatemia in all HIV-infected individuals. This confirms the disruption of phosphocalcic balance reported by Boyvin et al. [6]. This situation is thought to be due to vitamin D deficiency [23] as observed in this study among PLHIV. The hyperphosphatemia is thought to be due to a low serum concentration of parathyroid hormone (PTH) and the inhibitory action of FGF-23 on α-1-hydroxylase. As a result, there will be no phosphate reabsorption in the proximal tubule [24]. The hyperphosphatemia observed in some PLHIV could also be due to the release of phosphorus into the bloodstream after bone resorption [25]. Thus, a direct effect of HIV on osteogenic cells has been reported, persistent activation of pro-inflammatory cytokines, upregulation of TNF-alpha that induces apoptosis in the osteoblast model [26]. In addition, although HIV-infected patients in this study had serum creatinine levels within normal range, subclinical renal dysfunction affecting hydroxylation can't be ruled out [23]. Indeed, the metabolism of vitamin D and that of parathyroid hormone are linked [27]. The hydroxylation of 25 (OH) D_3 to 1,25 $(OH)_2$ D_3 is strictly regulated by PTH, calcium and phosphorus to prevent the development of hypercalcemia. In addition, calcium reabsorption in the kidney is stimulated by 1,25 $(OH)_2$ D_3 under the influence of PTH [28]. However, the parathyroid hormone concentrations in this study are normal. They could not therefore be involved in this disruption of the phosphocalcic balance.

This 25 (OH) D_3 deficiency affected 50% of treated PLHIV and approximately 12% of untreated PLHIV. These results are similar to those of Ansemant et al.[29] who reported a deficiency of 25 (OH) D_3 in 50% of treated PLHIV. Similarly, a deficiency was observed in approximately 12% of HIV negative controls and insufficiency in 44% of controls. Sufficiency in 25 (OH) vitamin D reserves observed in our study could be explained due to the fact that Côte d'Ivoire is a tropical country with heavy sunshine, the major intakes pathway of vitamin D is through

Table 1. Mean values of biological parameters of the study population

Parameters	Control (N=163)	Treated patients (N=120)	Untreated patients (N=43)	*P* value a	*P* value b	*P* value c
Age (years)	31 ± 0.67	39 ± 0.63	32 ± 1.23	< 0.0001*	0.3169	< 0.0001*
Alkaline Phosphatase (40 – 129 UI/L)	77± 1.75	122±16.84	100 ± 5.18	0.0026*	< 0.0001*	0.2954
Calcium (2.2 – 2.7 mmol/L)	2.5± 0.04	2.9 ± 0.04	2.7 ± 0.04	< 0.0001*	0.0163*	0.0030*
Phosphorus (0.90 – 1.45 mmol/L)	1.19±0.03	2.55± 0.37	1.97 ± 0.25	< 0.0001*	< 0.0001*	0.1948
Magnesium (0.65 – 1.15 mmol/L)	0.78± 0.01	0.86± 0.01	0.78 ± 0.02	< 0.0001*	0.6594	0.0002*
Alanine aminotransferase (7 - 48 UI/L)	17 ± 1.00	23 ± 1.63	18 ± 0.83	0.0031*	0.8027	0.0171*
Glycemia (4.16 - 6.11 mmol/L)	5.00 ± 0.11	4.95±0.05	4.84 ± 0.11	0.8279	0.5521	0.4240
Creatinine (53 - 106 µmol/L)	70.8 ±1.59	70.8± 2.30	70.8 ± 2.74	0.6113	0.6653	0.4389
Urea (1.66 - 5.83 mmol/L)	4.65 ± 0.17	4.48±0.33	3.82 ± 0.33	0.4652	0.0065*	0.1772

*a: Control versus treated Patients; b: Control versus untreated Patients; c: Treated Patients versus Untreated Patients; * Pdenotes statistically significant value; The difference is significant for P< 0.05*

Table 2. Distribution of the study population according to 25 (OH) D_3 and parathyroid hormone status

Parametres	Control (N=163)		Treated Patients (N=120)		Untreated patients (N=43)	
	Number (%)	Mean value	Number (%)	Mean value	Number (%)	Mean value
25 (OH) D_3						
Deficiency < 20 ng/mL	19 (12 %)	14 ± 0.51	60 (50 %)	16 ± 0.46	5 (12 %)	19 ± 0.12
Insufficiency 20 - 30 ng/mL	72 (44 %)	28 ± 0.28	40 (33 %)	26 ± 0.35	18 (42 %)	26 ± 0.37
Sufficiency≥ 30 ng/mL	72 (44 %)	38 ± 0.96	20 (17 %)	44 ± 1.40	20 (46 %)	50 ± 1.65
Parathyroid hormone						
Insufficiency < 10 pg/mL	0 (0 %)	0	12 (10 %)	7 ± 0,21	0 (0 %)	0
Normal 10 - 65 pg/mL	157(96 %)	25 ± 1.69	104 (87 %)	28 ± 1.95	43 (100 %)	25 ± 2.09
Elevated > 65 pg/mL	6 (4 %)	80 ± 0.15	4 (3 %)	102 ± 0.18	0 (0 %)	0

Normal reference value of 25 (OH) D_3: 30 – 100 ng/mL

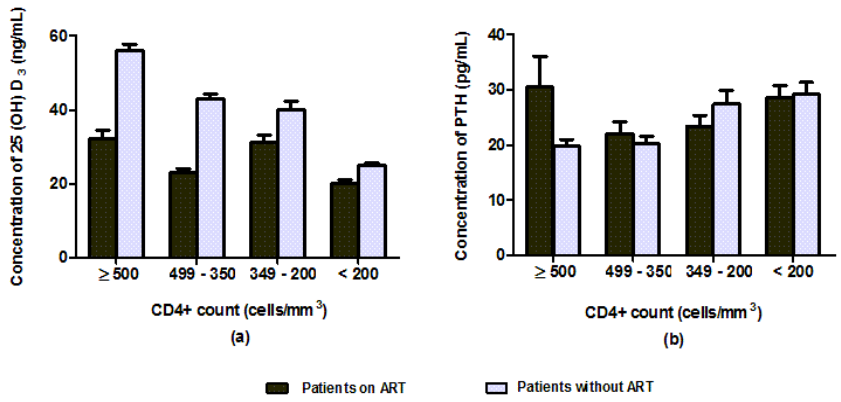

Fig. 1. 25 (OH) D_3 (a) and PTH (b) status according to CD4+ count

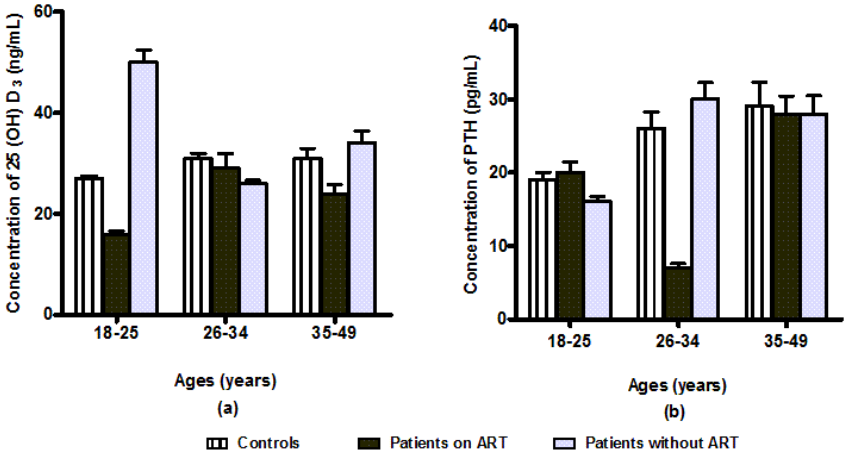

Fig. 2. 25 (OH) D_3 (a) and PTH (b) status according to ages

skin synthesis [30,31]. But the deficiency cases observed in control subjects may be due to the consumption of diets poor in vitamin D or other factors, since its supply has two sources (food and synthesis) [32]. Hypovitaminosis D is a global disorder, with a high prevalence in the population from the developing and western countries [33]. Beyond genetic, racial, geographic and seasonal differences, this deficiency is thought to be due to insufficient consumption of foods containing vitamin D (e.g milk and dairy products, fish, eggs and enriched orange juice) [34]. Furthermore, other factors such as female sex, age, dark skin pigmentation, body mass index (BMI), gastrointestinal absorption disorders -intestinal, risk factors for multiple cardiovascular diseases, including diabetes mellitus, co-infections including HIV / tuberculosis (TB), HIV / hepatitis C virus (HCV), renal and/or hepatic pathologies such as cholestatic hepatitis and current alcohol consumption are cited as risk factors for traditional hypovitaminosis D in seropositive and seronegative cohorts [13]. According to studies, even healthy people, exposed to adequate sunlight, can't synthesize enough vitamin D without supplementation [35,36]. Moreover, 25 (OH) D_3 insufficiency was found in 33% of treated PLHIV and 42% of untreated PLHIV. Gichuhi et al. [37] also found 25 (OH) D_3 insufficiency in 32.78% of treated PLHIV and 35.09% of untreated PLHIV. Indeed, in case of advanced HIV infection, a proinflammatory state is observed. Certain cytokines (INF-Y, IL-4) which are then secreted interact with cytochrome CYP27B1 which is a catalyst for renal 1α-hydroxylase [38]. This study showed insufficiency and deficiency in 25 (OH) D_3 in

treated PLHIV, in the range of CD4 T cell count of 499 - 350 cells / mL and less than 200 cells / mL respectively.

In this range of CD4, the occurrence of opportunistic infections highly increases the production of pro-inflammatory cytokines including TNF alpha (Tumor Necrosis Factor alpha) which inhibit 1-alpha -hydroxylase at the renal level thus stopping the transformation of 25 (OH) 2 vitamin D into its active form 1-25 (OH) vitamin D [39]. But also antiretroviral drugs especially IP and INNTI are highly inhibitory of cytochrome P450 and 25- and 1-alpha-hydroxylase enzymes [40]. Indeed, vitamin D is essential for maintaining phosphocalcic homeostasis. It also exhibits an immune defense regulatory activity and the ability to modulate the differentiation and proliferation of certain cell types that expresses the vitamin D receptor (VDR).

Untreated patients also showed insufficiency in 25 (OH) D_3 in the CD4 + T cell count range of less than 200 cells / mL.In general, in this range of CD4 T cells, infectious complications resulting from poor immunity require hospital care, which significantly reduces the duration of sun exposure for patients. Moreover, these infectious complications and hospitalization can lead to malnutrition and decreased oral consumption of certain foods containing vitamin D [13].

Therefore, this deficiency or insufficiency of vitamin D would disrupt immune system function and response. It would precipitate the destruction of CD4 and the progression of the disease [41]. Other authors have also found a positive association between vitamin D and CD4 counts [42]. In addition, deficiency in circulating vitamin D_3 could also be explained by variations in the locus encoding Vitamin D Receptor (VDR) during HIV infection [43]. VDR dysfunction related to 25 (OH) D_3 deficiency [44] is associated with progression of HIV infection [43,45].

In the present study, hypoparathyroidism (< 10 pg/mL) was observed only in 10 % (12/120) of treated patients. It should be noted that a decrease in the rate of PTH has already been reported in HIV infected patients [46]. The mechanism could be related to antibodies against parathyroid cells. Using anti-Leu3a, a monoclonal antibody that recognizes CD4, it has been found that HIV-positive patients have a CD4 molecule on the surface of parathyroid cells, indicating the possibility of functional inhibition by antibody anti-CD4 or direct HIV infection [47]. In addition, TNF-α appears to interfere with the stimulatory effect of PTH by mechanisms involving downregulation of PTH receptors, alteration of protein kinase C activity, and inhibition of cAMP response after PTH stimulation [23]. In addition, hyperparathyroidism was observed in 3% (4/120) of treated PLHIV against 4% (6/163) in HIV- negative controls. Studies have indicated that even a slight reduction in 25 (OH) D_3 serum levels may be associated with secondary hyperparathyroidism, increased bone renewal, and accelerated bone loss. This increases the risk of bone fractures [48]. In this study, the level of PTH is normal in all ranges of CD4 + T cells count in both treated and untreated patients. Although a high PTH concentration is considered characteristic of hypovitaminosis D, a "normal" concentration of PTH can be found in subjects classified as "vitamin D deficient". Therefore, although many subjects with 25 (OH) D_3 serum levels below the threshold may have PTH in the "normal" reference range, they may have "functional hyperparathyroidism" [49]. Thus, hypovitaminosis D may be considered a major risk factor for bone health [50].

5. CONCLUSION

This study showed that parathyroid hormone levels were normal in the population. They could not therefore be involved in phosphocalcic balance disruption. Furthermore, 25 (OH) D_3 deficiency was more common in treated patients, especially those with CD4 counts below 200 cells / mm^3 and age range 18-25 years. This disruption of 25 (OH) D_3 could be due to insufficient dietary intake of vitamin D-rich foods and not a parathyroid hormone-related defect. Deficiency of 25 (OH) D_3 could also be due to dysfunction of the vitamin D nuclear receptor (VDR). It would be interesting to further study the nuclear receptor of vitamin D (VDR).

ETHICAL APPROVAL

The study was conducted in accordance with the Helsinki 2000 Declaration on HIV and AIDS Research in Poor Countries and in accordance with local legislation on the National Program for the Care of People Living with HIV/AIDS (Decree No. 411 of 23 December 2001). Furthermore, for the research, consent was obtained from individuals for the use of their blood samples collected during biological monitoring.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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