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Metabolic Disorders of Vitamin D and Parathyroid Hormone in Patients Living with Human Immunodeficiency Virus Type 1 Taking Antiretroviral Treatment in Côte d'Ivoire

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Authors' contributions

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

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ABSTRACT

Background: A number of studies have highlighted the phosphocalcic balance disorder and posed the problem of the correlation between 25-hydroxyvitamin D_3 and parathyroid hormone in people living with HIV (PLHIV). However, few studies have been conducted on the link between antiretroviral therapy and the level of 25 (OH) D_3 during HIV infection. The objective of this study was to evaluate 25 (OH) D_3 and the parathyroid status in HIV-infected people taking antiretroviral treatment in Côte d'Ivoire.

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Methods: The study involved 326 adults (163 HIV-infected patient and 163 control subjects). CD4 count was performed in flow cytometry. 25 (OH) D_3 was assayed by HPLC. Parathyroid hormone was assayed using COBAS 6000.
Results: The deficiency of 25 (OH) D_3 was observed in patients aged 18 to 25 years and in patients on AZT-3TC-EFV (13 ± 0.68 ng / mL), AZT-3TC-NVP (11 ± 0.15 ng / mL) and TDF-3TC-EFV (19 ± 0.57 ng / mL). Sufficient levels of 25 (OH) D_3 were observed in patients receiving TDF-3TC-LPV/r. 25 (OH) D_3 deficiency was observed in women receiving AZT-3TC-EFV, AZT-3TC-LPV/r or TDF-3TC-EFV and men receiving AZT-3TC-NVP or AZT-3TC-LPV/r. The levels of PTH were normal in all patients aged 26 to 34 years and treated with AZT-3TC-EFV (9 ± 0.08 pg / mL), AZT-3TC-NVP (7 ± 0.21 pg / mL) or TDF-3TC-EFV (8 ± 0.25 pg / mL). Patients with CD4+ count between 349 and 200 cells / mm^3 and patients who were treated with AZT-3TC-NVP (7 ± 0.21 pg/ mL) also had normal PTH levels.
Conclusion: Some antiretroviral combinations prescribed in Côte d'Ivoire induce a decrease in the serum level of vitamin D and parathyroid hormone in PLHIV. It would, therefore, be necessary to add a vitamin D supplement when prescribing these combinations, considering its importance in cellular metabolism.

Keywords: 25 (OH) D_3; Côte d'Ivoire; parathyroid hormone; antiretroviral therapy; HIV1.

ABBREVIATIONS

$1,25(OH)_2D_3$: 1,25-dihydroxyvitamin D_3
$25(OH)D_3$: 25-hydroxyvitamin D_3
BMI : Body Mass Index
CYP : Cytochrome P450
PTH : Parathormone
CYP27B1 : Cytochrome 27 B1
cART : Combined Antiretroviral Therapy
PLHIV : Person Living with HIV
VDR : Vitamin D Receptor
cAMP : Cyclic Adenosine Monophosphate

1. INTRODUCTION

The human immunodeficiency virus type 1 (HIV 1) has infected 76.1 million people and had caused 35 million deaths worldwide by the end of 2016 [1]. Today, highly active antiretroviral therapy (HAART) has profoundly altered the natural history of HIV infection by dramatically reducing AIDS-related morbidity and mortality [2] and restoring immunological function by suppressing viral load [3]. However, until now, triple antiretroviral therapy cannot eradicate HIV [2,4]. Many studies have reported high early mortality in patients taking antiretroviral therapy in sub-Saharan Africa [5].

During the different stages of HIV infection, increased consumption of vitamin D has been demonstrated. The primary role of 25-hydroxyvitamin D_3 (25 (OH) D_3) is the regulation of calcium and phosphate homeostasis [6,7] in combination with parathyroid hormone (PTH) and calcitonin [8]. 25 (OH) D_3 is used in the differentiation of cells of the immune system that undergo greater renewals during HIV infection [9]. It is also highly recognised as an immunomodulator. It regulates the pathways involved in killing intracellular pathogens and modulates T cells, cytokines and dendritic cells [10]. Vitamin D deficiency is common among HIV-positive people [11]. This micronutrient has well-known regulatory functions in calcium metabolism, regulation of the pathways involved in killing of intracellular pathogens and modulates T cells, cytokines and dendrite cells [10].

Previous studies have reported a link between antiretroviral therapy and the serum level of 25 (OH) D_3 [3,12]. In Côte d'Ivoire, few studies have been conducted on the link between antiretroviral therapy and the serum level of 25 (OH) D_3 during HIV infection. Boyvin et al. [13] have highlighted the disorder in the phosphocalcic balance and the issue of the correlation between 25-hydroxyvitamin D_3 and parathyroid hormone in people living with HIV (PLHIV).

The objective of this study was to evaluate the issue of 25-hydroxyvitamin D_3 and parathyroid status of the people living with HIV (PLHIV) taking antiretroviral treatment in Côte d'Ivoire.

2. MATERIALS AND METHODS

2.1 Study Population

The study was started in November 2016 and continued till December 2017 in the Department of Basic and Medical Biochemistry of the Institute Pastor of Côte d'Ivoire (IPCI). The study involved 326 adults subjects aged 18 to 49 years. It was a cross-sectional descriptive study of 163 HIV-infected patients (120 were on antiretroviral

therapy versus 43 untreated patients). Treated patients composed of 45 men and 75 women. 163 controls of HIV-negative subjects were included. Pregnant women and children under 15 years were not included in this study.

2.2 Collection of Blood Samples

Blood samples from fasting HIV-positive and HIV-negative subjects were required for the various biochemical and serological tests. Thus, EDTA tubes containing whole blood were used for CD4+ T cells count of PLHIV. A tube without anticoagulant was used for blood collection, and the serum obtained after centrifugation was used for the HIV serological test and the assay of 25-hydroxy vitamin D_3 and parathyroid hormone (PTH).

2.3 HIV Serological Tests

For the detection of anti-HIV antibodies, two rapid tests were used:

(1) The kit "Alere Determine ™ HIV-1/2 kit " which is an immunochromatographic screening test. It's principle is based on the formation of an antigen-antibody complex revealed after staining [14] and
(2) The rapid "SD Bioline HIV-1/2; 3.0" test which is a confirmatory enzyme immunoassay. This test is based on the detection of anti-HIV1 and anti-HIV2 antibodies directed specifically against their antigens [15].

2.4 Determination of Biological Parameters

The CD4+ lymphocyte count was performed in flow cytometry on the BD FacsCalibur system (BD Becton, Dickinson, USA) from whole blood collected in EDTA. The principle is based on the rapid analysis of moving particles (cells) moving one by one inside a sheath fluid, in front of a laser beam light [16,17].

The assay of the 25-hydroxyvitamin D_3 was performed using UV detection in high-performance liquid chromatography (HPLC) with a Water® device, after extracting soluble vitamins with hexane protected from light according to the method of Zaman et al. [18].

The parathyroid hormone assay was performed with the COBAS 6000 device (Roche Hitachi, Japan) following the manufacturer's instructions. The serum reference value of parathyroid hormone was 10 to 65 pg / mL [19,20].

2.5 Statistical Analysis

GraphPad Prism.V5.01 software was used for statistical analysis of the collected data. The data were analysed with one-way ANOVA. The Turkey test was used to compare the variance of HIV-negative subjects with that of PLHIV. The difference between the two variances was significant if $p < 0.05$.

3. RESULTS

3.1 Mean Serum Level of 25 (OH) D_3 and PTH of the Study Population

At the end of this study, blood samples from 326 individuals including 163 HIV-infected patients and 163 HIV-negative people were analysed. Among these 163 HIV-infected patients, 120 were taking antiretroviral therapy and 43 patients were not taking ART.

Significant insufficient serum level ($p < 0.0001$) of 25 (OH) D_3 was observed between ART treated HIV positive patients (120) and ART untreated HIV patients (43) (Table 1).

The average PTH serum level was normal in this study (Table 1).

3.2 Mean Serum Level of 25 (OH) D_3 and PTH in Patients Taking Antiretroviral Therapy

Table 2 indicates a normal serum level of PTH in all the treated patients, according to the gender and type of combined antiretroviral therapy. This population was characterised by an insufficiency of 25 (OH) D_3. However, a deficiency of 25 (OH) D_3 (19 ± 1.55 ng/ml) was observed in 21 (17.5%) patients treated with the combination Zidovudine / Lamivudine / Efavirenz (AZT-3TC-EFV). In addition, sufficient serum levels of 25 (OH) D_3 were observed in patients treated with TDF-3TC-LPV/r (32 ± 1.22 ng / mL) (Table 2).

3.3 Vitamin D and PTH Status of PLHIV According to Gender and Type of Antiretroviral Therapy Taken

In women

According to Fig. 1.a, patients taking TDF-3TC-LPV/r had a normal serum level of vitamin D.

However, vitamin D deficiency was observed in those who were taking AZT-3TC-NVP. On the other hand, vitamin D insufficiency was observed in those who were treated with AZT-3TC-EFV, AZT-3TC-LPV/r or TDF-3TC-EFV combinations (Fig. 1a). PTH serum levels were normal regardless of the combination of antiretroviral taken, as all were higher than 10 pg / mL, despite of the decrease seen in TDF-3TC-LPV/r treated women (Fig. 1b).

In men

Fig. 2a depicts that patients receiving AZT-3TC-EFV and TDF-3TC-EFV had a deficiency of vitamin D (< 20 ng /mL). However, vitamin D deficiency (< 30 ng / mL) was observed in the

Table 1. Mean value of 25 (OH) D_3 and PTH 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
25 (OH) D_3 (30 - 100 ng/mL)	31 ± 1.56	28 ± 2.20	48 ± 2.07	0.3776	< 0.0001*	< 0.0001*
PTH (10 - 65 pg/mL)	27 ± 2.26	25 ± 3.66	23 ± 2.12	0.8821	0.2982	0.5767

a : Control vs Treated Patients; b : Control vs Untreated Patients; c : Treated Patients vs Untreated Patients; * *p* indicates a statistically significant value. The difference is significant for $p < 0.05$. Normal reference values of 25 (OH) D_3 : 30 - 100 ng/mL; Deficiency < 20 ng/mL ; Insufficiency 20 - 30 ng/mL ; Sufficiency = 30 ng/mL ; Normal reference values of PTH : 10 - 65 pg/mL.

Table 2. Serum level of 25 (OH) D_3 and PTH of the population taking antiretroviral

PARAMETERS	Number (%)	25 (OH) D_3 (ng/mL)	PTH (pg/mL)
Gender			
Women	75 (62.5 %)	23 ± 1.21	26 ± 1.81
Men	45 (37.5 %)	23 ± 1.82	29 ± 3.86
Combination of antiretroviral			
AZT-3TC-EFV	21 (17.5 %)	19 ± 1.55	25 ± 0.98
AZT-3TC-NVP	40 (33.3 %)	24 ± 1.68	22 ± 2.31
TDF-3TC-LPV/r	11 (9.2 %)	32 ± 1.22	18 ± 0.27
AZT-3TC-LPV/r	11 (9.2 %)	28 ± 1.18	29 ± 0.60
TDF-3TC-EFV	37 (30.8 %)	22 ± 1.81	29 ± 4.19

AZT : Zidovudine or 3'-azido-3'-dideoxythymidin; 3TC : Lamivudine; EFV : Efavirenz ; TDF : Tenofovir disoproxil fumarate; LPV/r : Lopinavir/ritonavir ; Normal reference value s of 25 (OH) D_3 : 30 - 100 ng/mL; Deficiency < 20 ng/mL ; Insufficiency 20 - 30 ng/mL ; Sufficiency = 30 ng/mL ; Normal reference values of PTH : 10 - 65 pg / mL

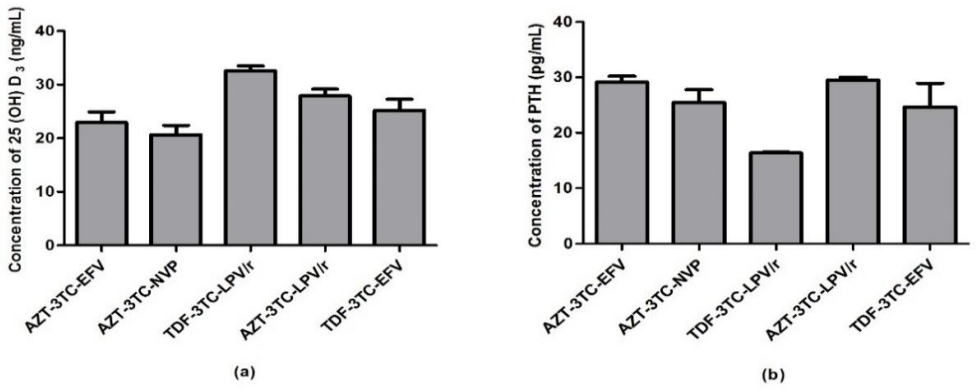

Fig. 1. Serum level of 25 (OH) D_3 (a) and PTH (b) of HIV-infected women taking antiretroviral therapy

patients taking AZT-3TC-NVP and AZT-3TC-LPV/r. In contrast, those treated with the combination TDF-3TC-LPV/r were characterised by vitamin D sufficiency (Fig. 2a). PTH levels were normal regardless of the combination of antiretroviral taken, although a decrease was observed in those treated with AZT-3TC-EFV, AZT-3TC-NVP and TDF-3TC-LPV/r (Fig. 2b).

3.4 Vitamin D_3 and PTH Serum Level in Patients Treated According to Age, CD4 + T Cell Count and Antiretroviral Therapy

A deficiency of 25 (OH) D_3 was observed in patients treated with the combination of AZT-3TC-NVP (11 ± 0.15 ng / mL) aged 18 to 25 years and with a CD4 + T cell count below 200 cells / mm^3 (15 ± 0.17 ng / mL) (Table 3). Similarly, a 25 (OH) D_3 deficiency was observed in the patients treated with the combination of AZT-3TC-EFV (13 ± 0.68 ng / mL) and having a CD4 + T cell count below 200 cell / mm^3 on one hand, and those in the 499-350 cell / mm^3 range treated with the combination TDF-3TC-EFV (19 ± 0.57 ng / mL) on the other hand. However, in all subjects treated with the combination of TDF- 3TC-LPV/r, a sufficient serum level of 25 (OH) D_3 was observed regardless of the age and the level of CD4+ T cell count (Table 3).

Normal serum levels of PTH were observed regardless of age, CD4+ T cell count, and the type of antiretroviral therapy taken. However, PTH deficiency was observed in subjects aged 26 to 34 years treated with the combination AZT-

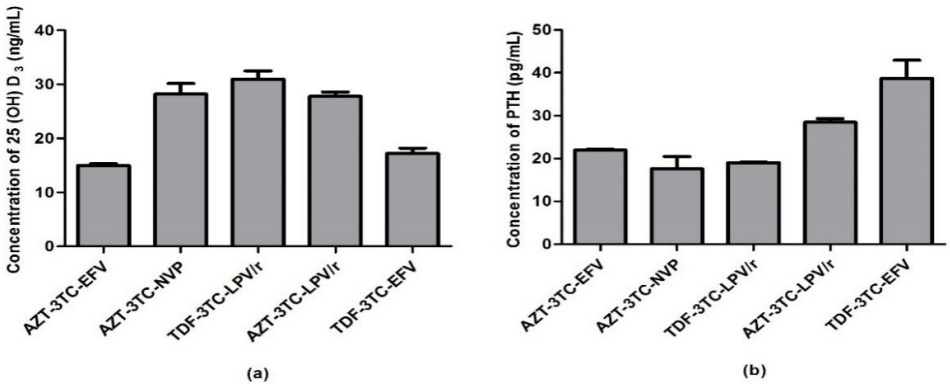

Fig. 2. Serum level of 25 (OH) D_3 (a) and PTH (b) of HIV-infected men taking antiretroviral therapy

Table 3. Average serum level of 25 (OH) D_3 and PTH according to age, CD4+ T count and antiretroviral therapy

PARAMETERS	AZT-3TC-EFV N = 21		AZT-3TC-NVP N = 40		TDF-3TC-LPV/r N = 11		AZT-3TC-LPV/r N = 11		TDF-3TC-EFV N = 37	
	25 (OH) D_3 (ng/mL)	PTH (pg/mL)	25 (OH) D_3 (ng/mL)	PTH (pg/mL)	25 (OH) D_3 (ng/mL)	PTH (pg/mL)	25 (OH) D_3 (ng/mL)	PTH (pg/mL)	25 (OH) D_3 (ng/mL)	PTH (pg/mL)
Age (years)										
18 - 25	0	0	11 ± 0.15	12 ± 0.13	0	0	33 ± 0.22	30 ± 0.09	22 ± 0.15	22 ± 0.12
26 - 34	23 ± 0.14	9 ± 0.08	28 ± 1.84	7 ± 0.21	41 ± 0.16	18 ± 0.16	0	0	27 ± 1.14	8 ± 0.25
35 - 49	26 ± 1.12	31 ± 0.86	29 ± 1.78	31 ± 3.19	33 ± 0.65	17 ± 0.27	30 ± 0.72	28 ± 0.77	27 ± 1.85	32 ± 4.16
Lymphocytes T CD4 count (cell/mm ^{3})										
> 500	35 ± 1.24	32 ± 0.47	30 ± 1.69	31 ± 3.76	33 ± 0.68	17 ± 0.42	28 ± 1.25	31 ± 0.15	22 ± 0.85	17 ± 2.12
499 - 350	25 ± 1.14	26 ± 1.72	21 ± 0.47	20 ± 1.03	32 ± 0.84	18 ± 0.17	22 ± 0.21	22 ± 0.21	19 ± 0.57	17 ± 4.17
349 - 200	23 ± 0.94	27 ± 0.94	34 ± 2.42	7 ± 0.21	35 ± 0.84	17 ± 0.17	31 ± 0.08	27 ± 0.61	28 ± 2.12	40 ± 3.89
< 200	13 ± 0.68	28 ± 0.25	15 ± 0.17	29 ± 0.59	37 ± 0.17	18 ± 0.21	0	0	20 ± 3.12	43 ± 3.39

3TC-EFV (9 ± 0.08 pg / ml), AZT-3TC-NVP (7 ± 0.21 pg / ml) or with TDF-3TC-EFV (8 ± 0.25 pg / ml). The same is true for those treated with the combination of AZT-3TC-NVP with CD4 + T cell count between 349 and 200 cells / mm^3 (7 ± 0.21 pg /ml) (Table 3).

4. DISCUSSION

In this study, a lower level of 25 (OH) D_3 was observed in patients taking ARV therapy compared to the patients not taking an ARV. These results are in agreement with those of Gichuhi et al. [21] who also reported lower 25 (OH) D_3 level in PLHIV taking ARV. Generally, vitamin D deficiency in HIV-infected individuals is linked to factors such as non-Caucasian race, high body mass index, hypertension, lack of physical exercise, decreased exposure to UV rays, decreased glomerular filtration [22], and poor absorption [12]. Similarly, several factors such as female gender, age, sun exposure, black pigmentation of the skin, non-Caucasian race, body mass index (BMI), gastrointestinal absorption disorders. Kidney disease, risk factors for cardiovascular disease (diabetes), co-infections such as HIV / TB (TB), HIV / hepatitis C (VHC) and daily alcohol consumption are cited as the natural risk factors for hypovitaminosis D in seropositive and seronegative cohorts [2]. In addition, previous studies have suggested that VDR gene polymorphism may be important for susceptibility to inflammatory diseases. Indeed, VDR gene polymorphism can negatively affect the 25 (OH) D_3 status [23]. According to Lake and Adams [24], antiretroviral therapy may also disrupt the metabolism of vitamin D. According to the National Health and Nutrition Examination Surveys (NHANES) database,, the prevalence of vitamin D deficiency according to age, race and sex was high in HIV-infected individuals (70%) but lower than US adults (79%) [22]. The circulation of vitamin D_3 deficiency could also be explained due to thevariations in the locus encoding VDR during HIV infection [25]. The dysfunction of VDR related to 25-hydroxyvitamin D_3 deficiency [26] is associated with the progression of HIV infection [25].

In this present study, a normal serum level of 25 (OH) D_3 was observed in some patients treated with TDF-3TC-LPV/r. However, certain patients treated with the combination AZT-3TC-EFV, AZT-3TC-NVP, AZT-3TC-LPV/r or TDF-3TC-EFV were characterised by a lower serum level of 25 (OH) D_3. Both protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been associated with the disruption of vitamin D metabolic pathways [27,28]. In general, NNRTIs, react with vitamin D through cytochromes (CYP3A4) required for vitamin D metabolism [11]. Thus, intake of efavirenz (EFV) has been associated with 25 (OH) D_3 deficiency [10,12]. Efavirenz lowers the level of 25 (OH) D_3 [3] by inducing the catabolism of 25 (OH) D_3 by the induction of cytochrome CYP24A, the enzyme that converts 25 (OH) D_3 to its inactive metabolite, namely 24,25-dihydroxyvitamin D_3 [2]. Contrary to NNRTIs, Nucleoside Reverse Transcriptase Inhibitors (NRTIs) are not metabolised by cytochromes [11]. Studies have shown that zidovudine is also associated with vitamin D deficiency [29]. This lower value of 25 (OH) D_3 is observed in some women treated with the combination AZT-3TC-EFV, AZT-3TC-NVP, AZT-3TC-LPV/r or TDF-3TC-EFV. Within the class of NNRTIs, a link with low vitamin D status has been reported in the case of efavirenz but not for nevirapine [30-32]. Some men who received the combination AZT-3TC-EFV, AZT-3TC-NVP, AZT-3TC-LPV/r or TDF-3TC EFV treatment were characterised by a lower vitamin D level. Generally, women are more exposed to vitamin D deficiency than men [33]. Adipose tissue is able to store vitamin D [34]; this could explain the lower serum level of 25 (OH) D_3 in women. However, it has long been shown that HIV infection induces the expression and secretion of IL-6 by monocytes and macrophages. Indeed, adipose tissue can produce, in some cases, up to 25% of circulating IL-6, proinflammatory cytokine [35]. According to Yilma et al. [36], patients who were treated with a combination of TDF-3TC-EFV and AZT-3TC-NVP had a lower 25 (OH) D_3 serum level after three months of treatment compared to TDF-3TC-NVP. In addition, all 11 patients treated with TDF-3TC-LPV/r, regardless of gender, age and CD4+ T cell count, had normal serum levels of 25 (OH) D_3 and PTH. These results are in agreement with that of Klassen et al. [37], who found normal serum levels of 25 (OH) D_3 and PTH in patients receiving TDF. In addition, intake of tenofovir or ritonavir has been shown to be associated with high serum levels of 25 (OH) D_3 [22]. Ritonavir appears to interfere with vitamin D metabolism by inhibiting 1α- and 25α-hydroxylation in both hepatocytes and monocytes in culture. Therefore, reducing the conversion of 25 (OH) D_3 to its active metabolite, this could potentially explain the increase of 25 (OH) D_3 in subjects with low concentrations of 1,25 $(OH)_2$ D_3 [38]. As for tenofovir, no known effect on vitamin D metabolism has been

reported. However, the combination of protease inhibitors (PIs) and tenofovir results in more deregulation of mineral metabolism than an alteration in the level of 25 (OH) D_3 [22]. In addition, tenofovir is known to induce renal proximal tubule dysfunction which may reduce the effect of 1α-hydroxylase in the kidney, which metabolises vitamin D to 1,25-hydroxyvitamin D in its active form, thus leading to accumulation of vitamin D [39]. This situation is associated with phosphaturia/hypophosphatemia, and 1,25 $(OH)_2$ D_3 is a hormone that counteracts hypo-phosphatemia. Therefore, it is possible that inhibition in the production of 1,25 $(OH)_2$ D_3 by protease inhibitors could exacerbate the deregulation of mineral metabolism in patients receiving tenofovir [22]. In this study, normal serum levels of PTH were found regardless of age, CD4+ T cell count and type of antiretroviral therapy. In some patients treated with the combination TDF-3TC-LPV/r, the PTH produced could not promote the conversion of 25 (OH) D_3 into 1,25 $(OH)_2$ D_3 (active form). However, the deficiency of PTH (hypoparathyroidism) was observed in patients aged 26-34 years treated with the combination AZT-3TC-EFV, AZT-3TC-NVP or TDF-3TC-EFV. It is the same for those who were treated with the combination AZT-3TC-NVP having CD4+ T cell count between 349 and 200 cell / mm^3. It should be noted that a decrease in the serum level of PTH has already been reported in HIV-infected patients [40]. The mechanism could be related to antibodies against parathyroid cells. Using anti-Leu3a, a monoclonal antibody recognising CD4, it was found that HIV-positive patients had a CD4 molecule on the surface of parathyroid cells, indicating the possibility of functional inhibition by anti-CD4 antibodies or direct HIV infection [41]. In addition, TNF-α appears to interfere with the stimulatory effect of PTH by mechanisms involving negative regulation of PTH receptors, alteration of protein kinase C activity, and inhibition of cyclic adenosine monophosphate (cAMP) response after PTH stimulation [42].

Furthermore, a lower serum concentration of 25 (OH) D_3 was reported in patients treated with the combination AZT-3TC-NVP aged 18 to 25 years and in those with a CD4+ T lymphocyte count below 200 cells / mm^3. This age group particularly is at risk. Indeed, in South Africa, 25 (OH) D_3 deficiency has been reported in patients aged 15 to 29 years. This situation has been observed in women aged 15 to 24 and in men aged 20 to 29 [43]. A deficiency in 25 (OH) D_3 was also observed in patients who were treated with the combination AZT-3TC-EFV and having a CD4+ T lymphocyte count of less than 200 cell / mm^3 on one hand, and those having CD4+ T lymphocyte count in the range 499-350 cell / mm^3 treated with the combination TDF-3TC-EFV on the other hand. Indeed, increased utilisation of vitamin D during HIV infection has been demonstrated. Vitamin D is used in the differentiation of immune system cells that undergo greater renewal during HIV infection [9]. It regulates the pathways involved in the destruction of intracellular pathogens and modulates T cells, cytokines and dendritic cells [10]. Its deficiency or insufficiency would hasten the destruction of CD4 and the progression of the disease [30]. Complicated Infections resulting from poor immunity (below 200 cell / mm^3) require hospitalisation, which significantly reduces patients' exposure to the sun. Also, this vitamin D deficiency observed in this study could be due to complicated infections and hospitalization, which could be responsible for malnutrition and reduced consumption of vitamin D-containing foods [2].

5. CONCLUSION

This study suggests that HIV-infected patients receiving antiretroviral therapy are at high risk of reduced serum level of vitamin D. However, some HIV patients treated with the combination TDF-3TC-LPV/r recorded normal serum levels of 25 (OH) D_3. In addition, PTH deficiency (hypoparathyroidism) was observed in some individuals aged 26 to 34 years treated with the combination AZT-3TC-EFV, AZT-3TC-NVP or TDF-3TC-EFV, and those who were on AZT-3TC-NVP with CD4+ T cell counts between 349 and 200 cell/mm^3. Therefore, vitamin D and PTH status should be checked regularly in all HIV-infected patients, taking into consideration the clinical stage.

CONSENT AND 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 the local legislation on the National Program for the Care of People Living with HIV / AIDS (Decree No. 411 of 23 December 2001). The blood samples were collected from HIV-positive patients for whom Pastor Institute of Côte d'Ivoire (IPCI) is a reference Laboratory and support centre for public health programs in Côte d'Ivoire in agreement with the Global Fund for AIDS, Tuberculosis and Malaria. In addition, for

research purposes, informed consents were obtained from individuals for the use of their blood samples taken in the course of biological monitoring.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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