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CLIMATE CHANGE, POLLUTION, TROPICAL SEASON, HIV-POSITIVE, HIV-NEGATIVE AND HIGH FREQUENCY OF HYPOVITAMINOSIS D IN PATIENTS FROM KINSHASA, DRC

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ABSTRACT

Background: The main source of vitamin D from the human skin and synthetized by violets B rays emitted by the sun. Environmental factors such us season, climate change, diets, and pollution, are therefore likely to influence the levels on vitamin D. Furthermore, High frequency of vitamin D deficiency is now observed among HIV-infected patients. There is no published data about HIV and Vitamin D despite few scientific articles on HIV and vitamin D status reported by other African countries.

Objective: This study sought to determine specifically increased prevalence of vitamin D deficiency and environmental factors associated with HIV-positive compared to HIV-negative.

Methods: Patients followed in Kinshasa hospitals, DRC, where evaluated between the October 2015 and November 2017 period. Serum levels of vitamin D were measured in adult HIV-positives and HIV-negatives during the dry season and the rainy season in the context of climate change and pollution of the megacity of Kinshasa.

Results: Five hundred and six patients were enrolled. The prevalence of moderate ($\leq$29 and $\geq$20 ng/mL) and severe (<20 ng/mL) 25-OH vitamin D deficiency was12% (n=64) and 54,6% (n=273) respectively, 34,4 %had normal status. 62,4% (n=316) and 4,2% (n= 21) of patients with deficiency (<30 ng/ml) 25-OH vitamin D were HIV-positive and HIV-negative respectively. Water pollution, air pollution, dry season, and cold season La Niña we resignificantly associated with 25-OH vitamin D deficiency ($P < 0.0001$ and <0,05, respectively).

Conclusion: Overall, vitamin D deficiency was very high whereas vitamin D deficiency was epidemic among HIV-positives in comparison with HIV-negatives. Dry season and La Niña season /climate change-variability related to ultraviolet light and oxidative stress-ecotoxicity related pollution might be considered in the prevention and the treatment of HIV-infection in Kinshasa, DRC, Central Africa.

KEYWORDS : Vitamin D, HIV infection, dry season, La Niña, climate change, DRC, Central Africa

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INTRODUCTION

Despite being closer to the equator with adequate Ultraviolet (UV) radiation, developing countries like those of sub-Saharan Africa are facing high prevalence of vitamin D disorders [1,2]. In sub-Saharan African countries, the prevalence of vitamin D disorders is estimated to be of 30% and associated with high morbidity and mortality [3,4]. Indeed, in addition to be directly involved in bone disorders, there is growing evidence supporting the association of Vitamin D (Vit D) disorders with diseases not related to bones, such as cardiovascular diseases (CVD) [1,2,5]. Therefore, early identification and control of Vitamin D disorders among at high risk groups such as people living with human immunodeficiency virus (HIV), could help reducing Vit D disorders-associated high morbidity and mortality [1,2,6]. Indeed, based on a large number of epidemiological studies using different Vit D thresholds, a recent review article showed that the prevalence of Vit D deficiency in HIV-infected patients ranges from 70% to 85% [7,8]. Non-HIV related factors, such as limited sunlight exposure as well as HIV-related ones, such as chronic inflammation, comorbidities, antiretroviral therapy are associated with vitamin D deficiency in persons living with HIV (PLWHIVs) [7,8]. HIV related Vit D deficiency has been found to negatively impact on disease acquisition, progression, response to therapy and outcomes [9,10]. Vitamin D deficiency might also interfere with immune restoration following highly active antiretroviral therapy (HAART) and exacerbate HIV-related disease complications in PLWHIV from Sub-Saharan Africa [11]. Therefore, early identification of the burden of Vit D disorders and control of associated risk factors could help improving outcomes in HIV-infected patients, mainly in Sub-Saharan Africa where the burden of both HIV-infection and Vit D disorders are very high [1,2]. In the Democratic Republic of the Congo (DRC), Vit D concentrations were compared between different groups from Kinshasa without Vit D disorders in the general population [12]. However, there is evidence on significant association between uterine leiomyoma [13], breast cancer (data not published) [14 Osongo], diabetic retinopathy [15], asthma in adult [16], and Vit D deficiency.

Moreover, available data from certain Sub-Saharan Africa have yielded conflicting results regarding the association of Vit D disorders and HIV-infection. It is not yet published on Vit D and HIV-infection in DRC. Therefore, the objective of the present study was to assess the burden of Vit D disorders associated with demographic HIV and non-HIV related risk factors, particularly environmental factors among naive and treated HIV-infected patients in Kinshasa, the capital City.

MATERIALS AND METHODS

Study design

A multicentric cross-sectional and observational survey was undertaken between October 2015 to November 2017.

Study setting

The study sites were characterized by the following four health levels of patient management with the use of antiretroviral treatment (ART): Community ART station or level 1; Referral health center or level 2; General referral hospital or level 3; University hospital or level 4.

Of the 1,315 ART facilities scattered across DRC, 335 (25.7%) are located in Kinshasa which were eligible for this study. The inclusion criteria for the health settings were as follows:

- level 2-4 health settings that provide ART, defined based on available resources (health center, general referral hospital, university hospital);
- level 2-4 health settings that provide ART for adults.

Of the 335 health settings of the capital Kinshasa, 114 (34%) were not excluded, including maternities, pediatric services and community ART station. 8 health settings were randomly selected by simple random random draw (Centre Hospitalier Boyambi, Hôpital central de la Police Nationale Congolaise, Centre Bomoi de N'djili, Centre Hospitalier Kimbanguiste, Hôpital Général de Makala, Centre Médical de Kinshasa, Hôpital Général de N'djili, Cliniques Universitaires de Kinshasa).

Study population and sampling

The study population consisted in HIV-infected and non-infected patients taken care in the ART Centers selected for the study that met the following inclusion criteria: attending one of selected ARV care centers, age ≥15 years, known and confirmed HIV-positive or negative serologic status, ARV naïve or treated (≥2 weeks), informed signed consent.

The criteria for exclusion were as follows: treatment with vitamin D supplementation or for osteoporosis, complications associated with vitamin D deficiency/insufficiency, such as recent hospitalization, chronic renal failure, nephrotic syndrome, pancreatic failure, chronic liver disease, active hepatitis or cirrhosis, malabsorptive disorders, active malignancy, recent use (previous 3 months) of medications that alter vitamin D status (carbamazepine, systemic glucocorticoids, hormones, isoniazid, phenobarbital, phenytoin, or rifampicin)

DATA COLLECTION

Data collection was based on interview, analysis of the medical records, physical and laboratory examination. During the interview, data were collected on demographic characteristics (gender, age), socioeconomic status (SES, marital status, education, religion), social habits (current alcohol intake or smoking habit, physical activity), occurrence of opportunistic diseases, chronic diseases not related to HIV (arterial hypertension and/or diabetes), use or antiretroviral therapy (ART) in the previous three months.

LABORATORY DATA

HIV rapid serological test (Alere Determine™ HIV-1/2, Abbott) was used in all participants to confirm the presence of HIV specific antibodies. Determine test is one of the three HIV-tests used at first-line for HIV/AIDS screening in DRC [17].

Total 25-OH Vitamin D (D2 and D3) was measured by the ELISA (Enzyme Linked Immunosorbent Assay) method, which is an enzymatic colorimetric assay [18].

OPERATIONAL DEFINITIONS

The level of Kinshasa urbanization (Figure 1) were defined according to Lukunga district (Northwest of the capital and urban communes), Funa district (South of the city center and urban communes), Mont-Amba district (Southeast of city center and rural-urban communes) and Tshangu district (east of the capital and rural communes) [19].

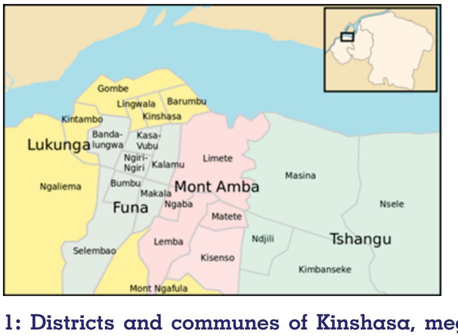

Figure 1: Districts and communes of Kinshasa, megacity (*source: Stanleyville.be*).

Socioeconomic status (SES) was defined by the low (unemployed, housewives, state officials) and high (traders, executives, legislators). Advanced age was defined as age

≥55 years. Marital status has been defined by single/non-married and married. Participants were belonging to Reveal-charismatic/Muslim churches or to traditional churches (catholic, protestant, Salvation Army and Kimbanguism churches).

Environmental factors included pollution, seasons (local climate), and climate change for global climate including climate variability. Air pollution in the City of Kinshasa Province was characterized by the residence near gas stations (lead), heavy road traffic (carbon monoxide, sulfur), industrial garages / factories, smoke near the mountains of waste in plastic, odors, dust [20]. The most exposed to atmospheric pollution were the communes of Bandalungwa, Barumbu, Kasa-Vubu, Bumbu, Gombe, Kalamu, Kinshasa, Kintambo, Kinsenso, Lingwala, Makala, Ngaba, Ngaliema and Selembao against communes less exposed to pollution (Kimbanseke, Lemba, Limete, Masina, Maluku, Matete and Nsele). Water pollution characterized water channels containing diesel and plastic-filled rivers accompanying floods responsible for erosions and landslides (fecal danger / nitrite and infections, lead, and cyanide) [21]. Same communes exposed to atmospheric pollution.

The local climate included the months of October, November, December, January, February, March, April and May for the rainy season, hot and humid, against the months of June, July, August and September for the cold and dry season.

Climate change is a global phenomenon characterized by a ceasing and continuous increase of heat by the emission of greenhouse gases (carbon dioxide, methane, nitrous oxide) [21]. This climate change is causing climatic variability in extreme heat values defining the 2015 and 2015 El Niño years against extreme cold values of the 2017 La Niña year [22]. Thus the period from October 2015 to December 2016 corresponded to the El Niño phenomenon, while the period from January to November 2017 corresponded to the La Niña phenomenon.

VitD status was defined normal or optimal status by a serum level of VitD ≥30ng/mL [23]. Hypovitaminosis D was defined by a serum level of vitD <30 ng/mL, vitD insufficiency for vitD=20 – 29 ng/mL and vitD deficiency for vitD ≤20 ng/mL [23].

ETHICAL CONSIDERATIONS

Research approval was obtained from the ethics committee of the Kinshasa University School of Public Health (No ESP/CE/062/2016) on 29 June 2016. All research procedures were undertaken according to the Helsinki. The participation in the study was voluntary, upon provision of a written informed consent form. Additionally, confidentiality of the information obtained from the participants was guaranteed and access to the study data was allowed only to the investigators.

DATA ANALYSIS

For categorical variables, data were presented as frequencies and proportions (%), whereas mean and standard deviations were used to present continuous variables.

In univariate analysis, Pearson's chi-square test was used to compare proportions between groups for large sample. Student's t-test was used to compare means between 2 groups for normally distributed variables. However, the analysis of variance (ANOVA) was performed to compare means for ≥ 3 groups.

After excluding confounding factors, a multivariable binary logistic regression analysis was performed to identify independent and significant determinant of hypovitaminosis D. A p-value <0.05 was considered as the threshold of statistical significance. All analysis was performed using the Statistical Package for Social Sciences (SPSS) version 23 for Windows.

RESULTS

In total, 506 participants were evaluated. The general characteristics were presented for all (HIV+ n=406 vs HIV- n=100) and compared between HIV+ and HIV- (Table 1). Sex ratio, age, tropical seasons admissions and El Niño/ La Niña years admission were similar (P>0,05) between HIV+ and HIV-. However, HIV+ patients were more frequent in hydric pollution and air pollution areas done their HIV- counterparts.

Table 1. Demographic and environmental Characteristics of the study participants

Variables	All (n=506)	HIV + (n=406)	HIV – (n=100)	P
Sex, % (n)				
Men	24.1 (122)	23.4 (95)	27 (27)	0.451
Women	75.9 (380)	76.6 (311)	73 (73)	
Age, % (n)				
> 60 yrs	58.9 (298)	59.6 (242)	56 (56)	0.512
< 60 yrs	41.1 (208)	40.0 (164)	44 (44)	
SES % (n)				
Low	75.5 (382)	87.2 (354)	28 (28)	< 0.0001
High	24.5 (124)	12.8 (52)	72 (72)	
Marital status, % (n)				
Married	70.2 (355)	79.6 (323)	32 (32)	< 0.0001
None married	29.8 (151)	20.4 (83)	68 (68)	
Churches, % (n)				
Reveal/Muslim	26.9 (136)	32.8 (133)	3 (3)	< 0.0001
Traditional churches	73.1 (370)	73.8 (273)	97 (97)	
Seasons, % (n)				
Dry	65,4 (331)	66 (268)	63 (63)	0,571
Rainy	34,6 (175)	34 (138)	37 (37)	
Hydric pollution, % (n)				
Yes	32,2 (163)	35,2 (143)	20 (20)	0,004
No	67,8 (343)	64,8 (263)	80 (80)	
Atmospheric pollution, % (n)				
Yes	47 (238)	53,7 (218)	20 (20)	< 0,0001
No	53 (268)	46,3 (188)	80 (80)	

Figure 2 summarizes the frequency of participants by climate variability / climate change: the majority of participants were admitted during El Niño 2015 - 2016 and rainy seasons without significant difference between men and women as well as between IHV+ and HIV- (results not presented).

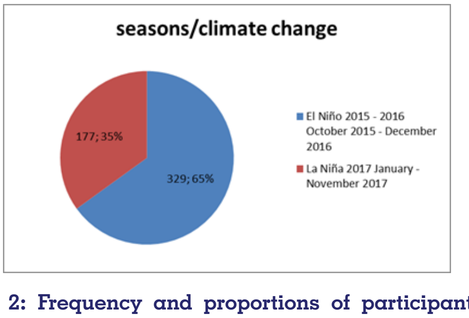

Figure 2: Frequency and proportions of participants by climate variability / climate change

The study population was characterized by residences Lukunga district (14,5% n=50), Funa district (16,5% n=57), Mont-Amba district (24,5% n=84) and Tshangu district (44,5% n=153).

Prevalence of hypovitaminosis D in study participants and according to HIV serological status

In the study population, hypovitaminosis D was estimated 66.6% (n=337/506), while considering the severity of hypovitaminosis D, 54.6% (n=273/506) participants had vitD deficiency, whereas 12% (n=64/506) had vitD insufficiency.

Highest, intermediate and lowest proportions of hypovitaminosis D were significantly (p<0.0001) reported in HIV+ not on ART (100% n=23/23), HIV+ on ART (76.5% n=64/23) and HIV- (21% n=21/100), respectively. Furthermore, when considering the HIV serological status of the study participants, a markedly higher prevalence of hypovitaminosis D was observed in the group of HIV infected patients (77.8% n=316/406), as compared with non-infected patients, the comparison group (21% n=21/100).

Associations between sociodemographic factors and hypovitaminosis D

Female, aging, churches of reveal, married status, low SES, HIV+ were identified as significant associated factors of hypovitaminosis D (Table 2).

Table 2. Associations between sociodemographics factors, HIV status and hypovitaminosis D

Variables	Hypovitaminosis D % (n)	OR (95% IC)	P Value
Sex			
· Female	69.3 (266/384)	1.6 (1.1 – 2.5)	0,024
· Men	58.2 (71/122)	1	
Age	76,8% (229/298)	3 (1,9 - 4,9)	<0,000
· ≥ 60 Yrs	51,9% (108/208)	1	1
· < 60 Yrs			
Churches			<0,000
· Reveal/Muslim	82,4 (112/136)	3,1 (2,1-4,5)	1
· Traditional churches	60,8 (225/370)	1	
Married status			
· Married	74,1 (263/355)	3 (2 - 4,4)	<0,000
· None married	49 (74/151)	1	1
SES			
· Low	76,4 (292/382)	5,7 (3,7- 8,8)	<0,000
· High	36,3 (45/124)	1	1
HIV statut			
· HIV+	77,8 (316/406)	13,2 (7,7-22,6)	<0,000
· HIV-	21 (21/100)	1	1

Associations between environmental factors and hypovita minosis D

Participants from Tshangu (rural) and Funa (urban) districts were more vulnerable (P<0,05) for hypovitaminosis D.
Participants exposed to water pollution (79.8% n = 130/163), air pollution (82.8% n = 197/238, admitted during dry season (89.1% n = 86/175), were more vulnerable to hypovitaminosis D than participants not exposed to water pollution (60.3% n = 207/343), air pollution (52.2% n = 140/268), dry season (rainy season: 75.8% n = 251/331), the differences being statistically very significant (P <0.0001).

With respect to the impact of climate variability/change, the La Niña cold period was more (P <0.05) associated with hypovitaminosis D (83% n = 144/177) than did the warm El Niño period (79.6% n = 262/329).

Independent role of environmental variables and HIV infection in the prevalence of hypovitaminosis D

After adjustment for sex, aging, churches, marital status, SES and residence, only positive HIV status, water pollution, dry season, and air pollution were identified as the most important significant and independent determinants of the prevalence of hypovitaminosis D in this study population (Table 3).

Table 3. Environmental determinants and HIV status on the prevalence of hypovitaminosis D

	Beta coefficient	Standard error	Wald Chi-square	Adj OR (95% CI)	Valeur P
independants Determinants					
HIV statut • HIV + • HIV-	2,808	0,328	73,333 Référence 1	16,6 (8,7-31,5)	<0,0001
Hydric pollution • Exposed • None exposed	0,887	0,285	9,7 Référence 1	2,4 (1,4-4,2)	0,002
Seasons • Dry • Rainy	1,435	0,254	31,991 Référence 1	16,6 (8,7-31,5)	<0,0001
Air pollution • Exposed • None exposed	0,992	0,249	15,930 Référence 1	16,6 (8,7-31,5)	<0,0001
Constante	- 3, 795	0,420	81,453	0,022	<0,001

DISCUSSION

The present study demonstrated significant socio-demographic and environmental factors at influencing epidemic hypovitaminosis D among patients from crowded and polluted Kinshasa megacity [21]. Indeed, the majority of patients residing in poorest Tshangu and Funa district [19].

As reported by several studies out [8,24], sub-Saharan Africa[25] and within Congolese [15,16] , the present study revealed high rate of prevalence of hypovitaminosis D in all closed to 70%, in HIV+ closed to 80% and in HIV- with 1/5 of participants.

Associated factors and determinants of hypovitaminosis D in univariate and multivariate analyses were used to identify potential factors associated (confusion bias) and independent determinants of hypovitaminosis D, respectively. As reported elsewhere [26-28], female gender, aging, churches of reveal, married status, low SES, poor districts (Tshangu and Funa), La Niña/climate change were identified as univariate associated factors of hypovitaminosis D in this study. HIV infection does reflect poverty (malnutrition, diarrhea, immune dysfunction) and might interact with female gender, aging, low SES and poor environment [29,30,31]. Among those covariables in this study, the main independent determinants of hypovitaminosis D were HIV positivity, water pollution, air pollution and local dry season.

Some studies reported significant association between HIV positivity and hypovitaminosis D [32,33]. Indeed, history of HIV/AIDS, denutrition/low BMI, decreased levels of CD4 lymphocytes for immune dysfunction and use of certain antiretroviral therapy such as non-nucleoside reverse transcriptase inhibitor (NNRTI), are well established as significant risk factors of hypovitaminosis D [34]. However, few published data [35] did not reported significant association between HIV infection and hypovitaminosis D.

DRC and other African countries suffer from the most polluted air, probably because it combines human (anthroponic) factors (car traffic geam with used vehicles on diesel, fuel stations/lead, generators, industry, cooking mode or heating) and natural (dust, perticulate or sand) especially in megacities like Kinshasa [36]. These adverse effects of pollutant environment on the decrease in vitamin D concentration is explained by the fact that these pollutants, mainly atmospheric, form a screen layer in the atmosphere hindering the passage of UVB radiation, which can compromise the endogenous synthesis of vitamin D[37]. Air pollutants, especially ozone and particulate matter (PMs) can directly affect cutaneous production of vitamin D [38]. Furthermore, persistent organic pollutants (POPs) behaving like endocrine-disrupting chemicals (EDCs) may inhibit the activity of cytochrome P450 (CYP450) and indirectly can cause vitamin D deficiency through weight gain and dysregulation of thyroid hormones, parathormone and caclcium homeostasis [37,38]. Environmental changes, including pollution and heat stress, have been reported to alter the immune system with subsequent altered vitamin D homeostasis [39]. Indeed, degraded environment produces fewer crops, at contributing to malnutrition and all its negative effects on immune system and vitamin D homeostasis [39].

Climate change as well as subsequent air and water pollutions could interfere with vitamin D metabolism through accelerated skin aging and altered immune function [39] already associated with hypovitaminosis D itself [3,6,27] and HIV infection itself [1].

The relationship between hypovitaminosis D and exposure to the dry and cold La Nina periods (accompanied by a low UVB radiation emission according to latitude) has been established by numerous studies [33,34,38,39].

Environmental changes also may foster conditions that are favorable for HIV transmission and progression, including many poverty related- and hypovitaminosis D related-infections that affect HIV-infected people, such as malaria and tuberculosis [40]. Indeed, in climate change/global warming each 2° to 3°C increase in ambient environmental temperature increases malaria transmission by 3% to 5% [25,40]. Coinfections-associated with immune activation and subsequent chronic oxidative stress and inflammation can lead to vitamin D deficiency in HIV-infected people [1].

IMPLICATIONS

Although living in areas exposed to Ultra-Violet B radiation and according to this study information, HIV-infected people should receive regular vitamin D dosing and vitamin D supplements especially during the dry season in the context of climate change, especially those living in polluted areas.

The present results will be used for research, training, prevention and control of coexisting HIV infection and hypovitaminosis D in tropical environment.

LIMITS AND STRENGTHS

The present study was limited to some degree because its cross-sectional design which did not establish a cause-and-effect relationship between identified determinants of hypovitaminosis D. indeed, only cohort studies and intervention (before and after) studies for supplement in vitD are able to demonstrate causal association. Thus, the present hospital findings are not to be generalized to the general population of Kinshasa. However, this is the first study to evaluate rigorously and scientifically the extent and determinants of hypovitaminosis D in both HIV-infected and HIV-uninfected patients across a representative sample of Kinshasa hospitals.

CONCLUSION

The extent of hypovitaminosis D and its severity is more marked in HIV infected patients than in non-HIV-infected individuals. La Niña cold period, positive HIV status, water pollution, dry season, air pollution are the factors associated with hypovitaminosis D in Kinshasa.

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