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Prevalence and risk factors of vitamin D deficiency among living with HIV adults receiving antiretroviral treatment in tropical area: Cross-sectional study

Jirayu Visuthranukul [a], Phenphop Phansuea [b,*,1], Pantat Buranakityanon [c], Prapawan Lerdrungroj [c], Eakkawit Yamasmith [a]

[a] Infectious Disease Unit, Department of Internal Medicine, Police General Hospital, Bangkok, 10330, Thailand
[b] Food and Nutrition Academic and Research Cluster, Institute of Nutrition, Mahidol University, Salaya, Phutthamonthon, Nakhon Pathom, 73170, Thailand
[c] Department of Internal Medicine, Police General Hospital, Bangkok, 10330, Thailand

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ABSTRACT

Background: There was found HIV infection have a higher rate of vitamin D deficiency (VDD) than the general population, even a slight deficiency, can increase the risk of osteoporosis in adults. This study aimed to determine the prevalence and risk factors of VDD in HIV-infected adults receiving antiretroviral therapy (ART) in a tropical area.

Methods: A cross-sectional study of an HIV-clinical population-based cohort was conducted at Police General Hospital (PGH), from 1st August 2020 to 31st July 2021, in Bangkok, Thailand. Serum 25(OH)D level was measured using ECLIA. All other laboratory investigations were conducted at the PGH's central lab center. The descriptive analysis utilized frequency (percentages) and mean (SD) as appropriate variable types. Chi-square tests ($\chi 2$) and independent samples t-tests were used to differentiate between VDD and non-VDD groups. To determine the association between VDD and non-VDD, gender, age (years), BMI discrepancy, ART regimens, ART-duration (years), HIV viral load, and CD4 count (cells/mm^3). Univariate and multivariable logistics regression was conducted, respectively.

Results: Of 602 patients, 66.4% were females with mean age of 45.22 ± 10.23 years. The average serum 25(OH)D level was 18.69 ± 7.23 ng/ml. The prevalence of VDD (<20 ng/ml) and insufficiency (VDI) (20–29.9 ng/ml) was 58.5% and 35.2%, respectively. Risk factors associated with vitamin D inadequacy were increasing age (AOR = 1.05, 95%CI = 1.03–1.07, P < .001), efavirenz (EFV-based) use (AOR = 6.07, 95%CI = 3.57–10.31, P < .001), while male (AOR = 0.44, 95%CI = 0.29–0.66, P < .001), body mass index (BMI) lower than 18.5 (AOR = 0.26; 95% CI, 0.11–0.62, P = .002), protease Inhibitors (PIs-based) use (AOR = 0.18, 95%CI = 0.11–0.30, P < .001),and CD4 count <200 cells/mm^3 (AOR = 0.41; 95% CI, 0.20–0.85, P = .017) were associated with less VDD.

Conclusion: The implementation of focused strategies for vitamin D supplementation, specifically targeting older patients and patients undergoing EFV-based ART regimen, can serve as a valuable addition to comprehensive HIV management. By optimizing vitamin D levels, there is a potential to improve health outcomes and enhance overall well-being for individuals living with HIV.

* Corresponding author.
E-mail address: phenphop.ph@gmail.com (P. Phansuea).
[1] Co-First author.

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1. Introduction

Vitamin D is a vital nutrient that assumes an indispensable role in optimizing bone health and bolstering the immune system. The human body obtains vitamin D from various sources, including sunlight, dietary intake, and Ergosterol supplements. Vitamin D is a collective term for vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), fat-soluble vitamins. Notably, vitamin D2 cannot be synthesized by the body itself and must be obtained exclusively through consumption. Vitamin D3 can be obtained from fatty fish such as salmon, sardines, mackerel, and tuna [1]. Endogenous production of vitamin D is made possible through the adequate dietary intake of vitamin D and exposure of the skin to ultraviolet-B radiation (UV–B) at the level of 290–315 nm [2]. The body undergoes intricate metabolic pathways to convert vitamin D into its principal circulating form, known as 25-hydroxyvitamin D (25(OH)D), as well as its hormonal form, recognized as 1,25-dihydroxy vitamin D (1,25(OH)2D). The liver and kidney predominantly carry out these conversions, respectively [3]. Nonetheless, it merits emphasis that additional tissues contribute to this metabolic cascade by engendering 1,25(OH)2D for localized functions. Illustrative instances of such tissues encompass the skin, immune system cells, parathyroid gland, intestinal epithelium, prostate, and breast. Nevertheless, low levels of vitamin D can precipitate the development of debilitating bone disorders, including rickets in infants and young children, as well as osteomalacia in adults. It is noteworthy that even a minor insufficiency in vitamin D levels exhibits a substantial elevation in the susceptibility to osteoporosis among adults [4].

According to the previous study conducted in Thailand in 2014, vitamin D deficiency (VDD, defined as serum 25(OH)D $<$ 20 ng/ml (50 nmol/L)) and vitamin D insufficiency (VDI, defined as serum 25(OH)D $<$ 30 ng/ml (75 nmol/L)) were both present at 5.7% and 45.2% of the population, respectively [5]. Although Thailand has year-round sunshine, latitudes are between 5°30′ N and 20°30′ N, VDI and VDD are still prevalent among the population. However, a higher prevalence of VDD has been observed among individuals infected with HIV compared to the general population [6]. Many previous studies investigating the relationship between low vitamin D levels and HIV infection suggests that VDD may have an impact on the progression of HIV infection or be influenced by the infection itself and its treatment [7,8]. The etiology of VDD in people with HIV is similar to that in the general population without HIV. However, it has been noted that several antiretroviral (ARV) drugs may contribute to the development of VDD [9]. Vitamin D metabolism involves the participation of the enzyme cytochrome P450 monooxygenase. Certain ARVs, such as efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitors (PIs), exert an influence on the enzymes involved in vitamin D synthesis. EFV, for instance, significantly induces CYP34 (25-hydroxylase) and CYP24 (24-hydroxylase), resulting in the hydroxylation of vitamin D3 to 25-hydroxyvitamin D3 (25(OH)D3) and the breakdown of 1,25(OH)2D to its inactive form [10]. EFV medication has also been associated with VDI in HIV- infected individuals. PIs inhibits the activity of the enzymes 25-hydroxylase and 1-hydroxylase in hepatocytes and monocytes. Vitamin D3 is hydroxylated to form 25(OH)D3 and 1,25(OH)2D3, respectively. Previous studies have found that nucleoside reverse transcriptase inhibitor (NRTI); tenofovir disoproxil fumarate (TDF) is associated with higher levels of parathyroid hormone, urinary phosphate loss, and bone mass loss, however there is no direct evidence of an association between TDF and altered vitamin D synthesis [11].

The prevalence of VDD among people living with HIV varies by country. In Spain, the prevalence is 71% [12], 70% in the United States [6], 39% in Australia [13], and 92.63% in Indian [14]. In Thailand, a cross-sectional study of VDD among 178 HIV-infected patients found that patients who were naïve and receiving antiretroviral therapy (ART) had mean serum 25(OH)D levels of 25 (±7.8) ng/ml and 26.9 (±9.9) ng/ml, respectively. The prevalence of VDD (25(OH)D $<$ 20 ng/ml) and VDI (25(OH)D 20–29 ng/ml) was 26.8% and 44.9%, respectively. It was found that people with HIV have a higher rate of VDD than the general population [13].

Several years have passed since the completion of the previous research, and there may now be a shift in factors. Taking into account that VDD is more prevalent among individuals infected with HIV compared to the general population, it is important to further enhance the efficacy of ART [15]. Therefore, the present study aims to assess the prevalence of VDD as well as the risk factors for VDD among Living with HIV Adults. The anticipated outcomes of this study are expected to furnish essential information for the formulation of guidelines pertaining to vitamin D supplementation in individuals with HIV, encompassing the identification of associated risk factors that are crucial for the implementation of preventive initiatives addressing VDD in HIV-infected adults receiving antiretroviral treatment in Thailand.

2. Materials and methods

2.1. Study design and ethics approval

A cross-sectional study of an HIV-clinical population-based cohort was conducted among HIV-1-infected patients visiting the HIV clinic Police General Hospital (HIV-PGH), from 1st August 2019 to 31st July 2020 (N = 1586) in Bangkok, Thailand. The STROBE checklist was used as a quality assessment tool. Data is analyzed after data cleaning, editing, documentation, and reviewing by the disclosure review board. The Police General Hospital Institutional Review Board reviewed and approved the study as number COA03/2020 and 56/2022.

2.2. Sample size calculation

The sample size was determined using Taro Yamane's formula [16], based on the total of antiretroviral-naïve patients in 2017, from the AIDS situation in Thailand report (N = 5529) [17]. The representative sample size needed is at least 373, with a margin error of 5%

and a confidence level of 95%. We intended to get more than the estimated sample size to account for any exclusions. The technique of convenience sampling was applied.

3. Recruitment procedures

3.1. Inclusion/Exclusion criteria

All patients older than 18 years who were diagnosed with HIV-1 during the study period were invited to participate. Patients will be excluded if they have the following criteria (1) stage 4, 5 of chronic kidney disease, (2) pregnancy conditions, (3) malignancies, (4) active granulomatous disease, (5) receiving vitamin D supplementation of more than 400 IU/day over 3 months before the study, (6) receiving anticonvulsants, rifampicin, and cholestyramine. History of HIV-1 infection, treatment, and laboratory data was obtained from medical records. At the time of registration, blood samples were collected for 25(OH)D measurement. However, the data is non-identified, so participants are not required to sign a written consent form.

3.2. Data acquisition

The HIV-PGH initiated the program. Official medical records are issued to all patients who visit the HIV-PGH department. Demographics are completed by a trained nurse team under physician supervision. Laboratory results and patient demographic information were gathered by the HIV-PGH electronic database, including age, gender, body mass index (BMI), type of ARV received, and length of time receiving ART. Laboratory investigations included serum levels of 25(OH)D, CD4 including HIV viral load. Blood collection was performed on the day of the examination or follow-up. Serum 25(OH)D level was measured using Electrochemiluminescence binding assay (ECLIA) on a Cobas e601 Analyzer (Roche Diagnostics Germany). All other laboratory investigations were conducted at the Police General Hospital's central lab center, using the same standardized machine and technique.

3.3. Statistical analysis

All statistical analyses were conducted using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). WHO and Asia-Pacific guideline for BMI was applied for the classification of BMI [18]. The Kolmogorov-Smirnov test was employed to assess the normality of the data distribution. Descriptive data were presented as means and standard deviations (SD) for continuous variables, and as counts and percentages for categorical variables. Categorical variables were assessed different between group using Chi-square tests ($\chi 2$) or Fisher's exact test, while continuous variables were evaluated using the independent samples *t*-test. To examine the impact of potential risk factors on 25(OH)D levels, Vitamin D will consider into binary levels (vitamin D deficiency group: Vitamin D $<$ 20 ng/ml;

Table 1
Demographic data of the participants (n = 602).

Characteristics	Total	Vitamin D $<$ 20 ng/ml (n = 352)	Vitamin D $\geq$ 20 ng/ml (n = 250)	*p* value
Age (years)	45.22 ± 10.23	42.73 ± 10.11	47.31 ± 9.33	<.001
Gender				.015
Male	400 (66.4)	220 (62.5)	180 (72.0)	
Female	202 (33.6)	132 (37.5)	70 (28.0)	
Body Mass Index (kg/m^2)	22.54 ± 3.49	22.31 ± 3.66	22.85 ± 3.22	.057
Underweight ($<$ 18.5)	56 (9.5)	48 (13.9)	8 (3.3)	<.001
Normal weight (18.5–22.9)	283 (48.0)	160 (46.2)	123 (50.4)	
Overweight (23.0–24.9)	100 (16.9)	50 (14.5)	50 (20.5)	
Obesity I (25.0–29.9)	151 (25.6)	88 (25.4)	63 (25.8)	
ART regimens				
Nucleoside/Nucleotide Reverse Transcriptase Inhibitor (NRTI)				
TDF + FTC/3 TC (TDF-based)	497 (82.6)	292 (83.0)	205 (82.0)	.761
AZT + 3 TC (AZT-based)	105 (17.4)	60 (17.0)	45 (18.0)	.761
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)				
Efavirenz (EFV-based)	568 (83.9)	327 (92.9)	178 (71.2)	<.001
Protease Inhibitors (PIs-based)	94 (16.1)	25 (7.1)	72 (28.8)	<.001
Duration of ART (years),	6.40 ± 3.29	6.06 ± 3.23	6.87 ± 3.32	.003
Median, IQR	7, (4–9)	6, (3–9)	8, (4–9)	
HIV viral load				.350
Undetectable	572 (95.0)	332 (94.3)	240 (96.0)	
Detectable	30 (5.0)	20 (5.7)	10 (4.0)	
CD4 count, cells/mm^3	524.65 ± 535.84	494.38 ± 243.95	567.28 ± 778.46	.100
Median, IQR	480, (346–604)	470, (331–613)	492, (360–396)	
$<$ 200 cells/mm^3	48 (8.0)	34 (9.7)	14 (5.6)	.049
200–350 cells/mm^3	112 (18.6)	72 (20.5)	40 (16.0)	
$>$ 350 cells/mm^3	442 (73.4)	246 (69.9)	196 (78.4)	

Note: Data expressed as a frequency (percentage) or the mean (SD) for categorical or continuous variables, respectively. Abbreviations: Antiretroviral therapy (ART).

non-vitamin D deficiency group: Vitamin D ≥ 20 ng/ml) [19] among HIV infection. Univariate analysis was employed to calculate the odds ratio (OR) and 95% confidence intervals (CI) for demographic data and type of antiretroviral treatment (ART) associated with HIV infection, with statistical significance defined as a p-value of .25. The independent effects of significant risk factors were determined using a multivariable logistic regression model. A p-value cutoff of 0.05 was utilized to determine statistical significance.

4. Result

There were 602 participants with a mean (SD) age of 45.22 (10.23) years and 66.4% of patients were males. It was found that the mean BMI was 22.53 ± 4.49 kg/m^2. Most participants had undetectable HIV viral load, median (IQR) of CD4 was 480 (346–604) cells/mm^3. Median (IQR) duration of ART was 7 (4–9) years. ART regimens received during the study showed that 82.6% received TDF-based regimen, 17.4% received AZT-based regimen, 83.9% received EFV-based regimen, and 16.1% received PIs-based regimen. There was no difference in VDD between HIV patients receiving ART who had undetectable HIV viral load and detectable HIV viral load. There was an association between the occurrence of VDD and CD4 when categorized. (Table 1).

The prevalence of VDD (<20 ng/ml) and VDI (20–29.9 ng/ml) was 58.50% and 35.20%, respectively. VDD was found to be high in HIV-infected women, with levels of VDD and VDI at 65.30% and 30.20%, respectively (Fig. 1). The distribution of vitamin D is as follows Table 2.

In univariate analysis gender, aging, higher BMI, taking efavirenz (EFV-based) regimen, protease inhibitors (PIs-based) regimen, duration of receiving ART, and CD4 count (<200 cells/mm^3) were the factors that had P < .25. In multivariable analysis, male gender, older age, BMI less than 18.5, and taking EFV-based regimen were significantly associated with the occurrence of VDD. Age increasing was found to be associated with VDD (Adjusted odds ratio (AOR = 1.05; 95% confidence interval (CI), 1.03–1.07, P < .001). Also, receiving EFV-based regimen was significantly associated with VDD (AOR = 6.07; 95% CI, 3.57–10.31, P < .001). However, the result showed that being male, having BMI less than 18.5, receiving PIs-based regimen, and CD4 count (<200 cells/mm^3) were significantly associated with less VDD occurrence (AOR = 0.44; 95% CI, 0.29–0.66, P < .001), (AOR = 0.26; 95% CI, 0.11–0.62, P = .002), (AOR = 0.18; 95% CI, 0.11–0.30, P < .001), and (AOR = 0.41; 95% CI, 0.20–0.85, P = .017) respectively. (Table 3).

5. Discussion

Despite Thailand's proximity to the equator and its abundance of year-round sunshine, there is an alarming prevalence of VDD among individuals living with HIV in the country. A national assessment conducted on healthy Thai individuals revealed a prevalence of VDD of approximately 6%, while a metropolitan study reported a significantly higher rate of 14% [20]. However, our research findings indicate an exceptionally high prevalence of VDD at 58.5% in living with HIV people. Furthermore, our study findings demonstrate a strong association between the use of EFV and the development of VDD. Specifically, compared to other ART regimens, EFV-based regimens were found to be six times more likely to lead to VDD (AOR = 6.07). This observation aligns with a previous study conducted in India, which reported a VDD prevalence of 66.93% among HIV-infected individuals treated with EFV [14].

Numerous prior studies have established that EFV elevates the activity of vitamin D-24-hydroxylase (24-OHase), an enzyme responsible for the degradation of 25[OH]D, thereby reducing its conversion to 1,25(OH)2D. EFV is also implicated in the suppression of 25-OHase enzymes, thereby impeding the conversion of vitamins D2 and D3 to 25(OH)D. Additionally, EFV primarily undergoes metabolism via the genetically polymorphic CYP2B6 enzyme, with some involvement from CYP3A enzymes. Vitamin D plays a role in regulating the expression of CYP3A and CYP2B6 enzymes. Notably, CYP3A catalyzes the 4-hydroxylation of 25(OH)D3, suggesting that

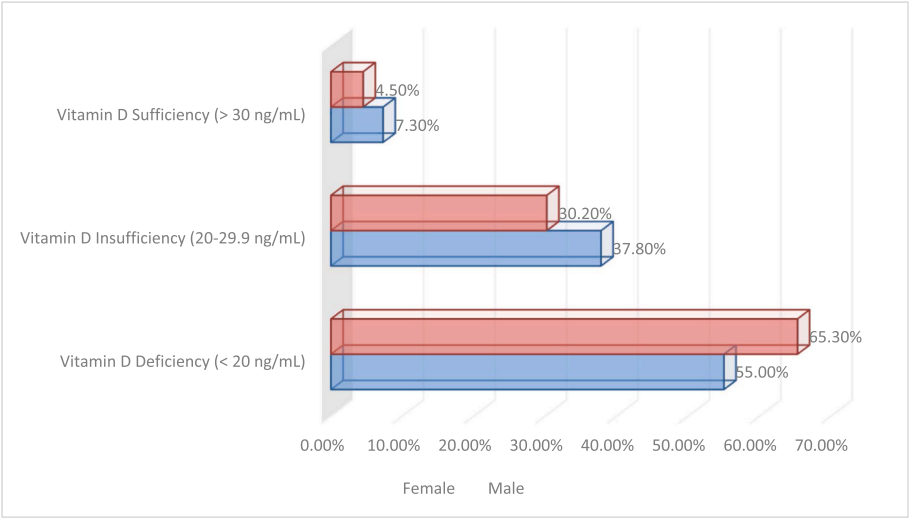

Fig. 1. Prevalence of vitamin D deficiency, vitamin D insufficiency, and vitamin D sufficiency by gender (n = 602).

Table 2
Distribution of vitamin D (n = 602).

Vitamin D level	N	%	M	SD	Min	Max
Vitamin D Deficiency (<20 ng/ml)	352	58.50	13.91	3.86	3.9	19.9
Vitamin D Insufficiency (20–29.9 ng/ml)	212	35.20	23.62	2.68	20.0	29.3
Vitamin D Sufficiency (>30 ng/ml)	38	6.30	35.40	4.87	30.0	45.9
Total	602		18.69	7.23		

Abbreviations: N, Number of participants; %, Percentages; M, Mean; SD, Standard Deviation; Min, Minimum; Max, Maximum

Table 3
Univariate and multivariable models of factors associated with vitamin D status.

Predictor	Univariate Model		Multivariable Model	
	Crude OR (95%CI)	*p* value	Adjusted OR (95%CI)	*p* value
Male Gender	0.65 (0.46–0.92)	.015	0.44 (0.29–0.66)	<.001
Age (years)	1.05 (1.03–1.07)	<.001	1.05 (1.03–1.07)	<.001
Body Mass Index (kg/m^2)	1.05 (1.00–1.10)	.063		
Underweight (<18.5)	0.23 (0.10–0.53)	<.001	0.26 (0.11–0.62)	.002
Normal weight (18.5–22.9)	1.07 (0.72–1.60)	.727	1.23 (0.79–1.93)	.366
Overweight (23.0–24.9)	1.40 (0.84–2.32)	.197	1.40 (0.80–2.45)	.215
TDF + FTC/3 TC (TDF-based)	1.07 (0.70–1.64)	.761		
AZT + 3 TC (AZT-based)	0.94 (0.61–1.43)	.761		
Efavirenz (EFV-based)	5.29 (3.24–8.64)	<.001	6.07 (3.57–10.31)	<.001
Protease Inhibitors (PIs-based)	0.21 (0.13–0.33)	<.001	0.18 (0.11–0.30)	<.001
Duration of ART (years)	1.08 (1.03–1.14)	.004	1.02 (0.96–1.09)	.482
HIV viral load	1.45 (0.67–3.15)	.352		
CD4 count (cells/mm^3)	1.00 (1.00–1.01)	.165		
<200 cells/mm^3	0.52 (0.27–0.99)	.047	0.41 (0.20–0.85)	.017
200-350 cells/mm^3	0.70 (0.45–1.07)	.100	0.77 (0.47–1.26)	.302

Abbreviations: Crude OR, Crude Odds Ratio; Adjusted OR (AOR), Adjusted Odds Ratio; CI, Confidence Interval

CYPdrug induced may contribute to drug-induced VDD [21–23]. In terms of HIV-specific factors, the current utilization of EFV has surpassed that of the past due to the combination of TDF-based (TDF + FTC/3 TC) and EFV-based regimens, which are now recommended as the initial treatment option for HIV according to the 2017 Thailand HIV treatment and prevention guidelines and the national list of essential medicines (NLEM) [24]. Given these circumstances, it is crucial to acknowledge the potential risk of VDD in individuals receiving this ART regimen.

Furthermore, our study identified a PIs-based regimen as a protective factor against VDD, with an 82% lower risk compared to individuals not utilizing this treatment. This finding aligns with a previous study conducted in 2012, which investigated the impact of vitamin D supplementation schemes in HIV-infected patients and found no significant effect of ART on serum D 25(OH)D levels when concentrations were adequate [25]. In addition, a study on the effect of calcium and vitamin D supplementation on bone mineralization in Thai adolescents with HIV and bone mineral density in 2018 showed that before and after taking the drug. The PIs-based regimens found no differences in bone mass and serum 25(OH)D levels for both treatment groups. NNRTI + PI and 1–2NRTI + PI [26].

An association between VDD and HIV patients with CD4 <200 cells/mm^3 was observed in our study. This finding aligns with previous studies that have indicated a correlation between VDD and CD4 levels in HIV patients with CD4 <200 cells/mm^3, suggesting that VDD may impede CD4 recovery following ART administration [27] Furthermore, reduced CD4 levels have been observed in patients who have not yet received ART [28]. However, it remains unclear whether there is a causal relationship between VDD and the incidence of low CD4 counts. Therefore, further investigations are needed to determine whether VDD negatively impacts CD4 recovery after ART treatment. It is of utmost importance to conduct further research in this domain to attain a more comprehensive understanding of the magnitude of this issue and to develop effective interventions and appropriate dosage guidelines for vitamin D. Also warranted to explore the optimal dosing strategies and long-term benefits of vitamin D supplementation in HIV patients on ART, particularly those on EFV-based regimens. By addressing VDD as part of comprehensive HIV care, healthcare providers can take initiative-taking steps to enhance the well-being and quality of life of individuals living with HIV.

Among the female population in our study, 65.3% (132:202) were VDD, which was five times greater than a study of HIV-infected pregnant women in Denmark (65.3%:13%) [29]. The cause of VDD may be due to factors common to VDD in today's culture that are different from those in the past, such as lifestyle habits that tend to avoid sunlight. Our study found that being male reduced the risk of VVD by 56% (AOR = 0.44). As previously stated, people today behave differently than in the past, especially Asian women, in particular, tend to avoid exposure to the sun [30] and though previous studies have shown that sunscreen use seems to have no effect on altered vitamin D levels, sun exposure avoidance habits may contribute to VDD and various diseases [19,31]. In addition, in 2019, the outbreak of COVID-19, the government has a policy to prevent the spread of infection from person to person by issuing the national and local containment policies, schools, Universities, companies, organizations and institutions encouraged their employees to work-from-home [32], causing most people to stay indoors for a long time. This is consistent with previous studies that reported that shift workers and indoor workers were most likely to be VDD [33].

In general, the cutaneous production of vitamin D declines with age. Aging is associated with a decrease in the concentration of 7-DHC in the skin, resulting in decreased vitamin D production. In our study, increasing age was identified as one of the risk factors for VDD. These findings are consistent with previous research indicating that older adults are more likely to experience VDD symptoms due to physical deterioration, decreased sunlight exposure, poor nutrition, and other factors [30]. Being overweight or having a high BMI is another risk factor for VDD. Our study reported that underweight groups (BMI<18.5) had a significantly 74% lower risk of developing VDD than obese groups (BMI>25) statistically significant. However, a previous study on vitamin D and obesity in 2021 continued to debate the relationship between obesity and VDD, arguing that there was a lack of clear reasons to explain the complex relationship [34].

This study possessed various limitations that necessitate careful consideration. Firstly, the sample size utilized in this study was limited to the patients of Police General Hospital, thereby implying that certain factors contributing to VDD may not be applicable to the entire population. Additionally, significant factors pertaining to VDD, such as sun exposure, UV radiation, and the patient's dietary and lifestyle habits concerning vitamin D intake, were not subjected to analysis within the scope of this study. Present research highlighting the prevalence and risks associated with HIV infection and VDD underscores the importance of addressing this matter. The administration of vitamin D replacement therapy may play a pivotal role in preventing complications in individuals living with HIV, particularly those undergoing ART.

6. Conclusion

The high prevalence of VDD in HIV patients on ART, even in tropical regions, underscores the importance of recognizing and addressing this deficiency. Implementing appropriate vitamin D supplementation strategies, especially for individuals on an EFV-based ART regimen, can serve as a valuable adjunct in the comprehensive management of HIV-infected patients. By optimizing vitamin D levels, healthcare providers can potentially enhance the health outcomes and quality of life for individuals living with HIV.

Author contribution statement

Jirayu Visuthranukul; Phenphop Phansuea: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Pantat Buranakityanon; Prapawan Lerdrungroj; Eakkawit Yamasmith: Performed the experiments.

Data availability statement

The data that has been used is confidential.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix B. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e19537.

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