Low Vitamin D and Kidney Function Decline among HIV-infected Adults in Thailand

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วิตามินดีที่ต่ำและการลดลงของการทำงานของไตในผู้ป่วยไทยที่ติดเชื้อเอชไอวี

วิน เหลียง ธานห์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต

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List of abbreviations

Ab	antibody
AR	attributable risk
ARV	antiretroviral drugs
ART	antiretroviral therapy
BMD	bone mineral density
BMI	body mass index
ºC	centigrade degree
CD4 cell	CD4 T cell
Cr	creatinine
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease and epidemiological collaboration
CMIA	chemiluminescent microparticle immunoassay
CMV	cytomegalovirus
DM	diabetes mellitus
DXA	Dual Energy X-ray Absorptiometry technique
EFV	efavirenz
ESRD	end stage renal disease
FBS	fasting blood sugar
GCP	good clinical practice
GFR	glomerular filtration rate
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIVAN	HIV-associated nephropathy
HIV-NAT	HIV Netherland, Australia and Thailand Research Collaboration

IES	International Endocrine Society
IRB	Institutional Review Board
MDRD	modification of diet in renal disease
MSM	men who sex with men
NRTI	nucleoside reverse transcriptase inhibitors
NNRTI	non-nucleoside reverse transcriptase inhibitors
NKF	National Kidney Foundation
OR	odd ratios
P	p value, calculated probability
PI	protease inhibitors
PI	principal investigator
PK	pharmacokinetics
RCT	randomized controlled trial
RR	relative risk or risk ratios
SCr	serum creatinine
SD	standard deviation
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
US	United States
Vit	Vitamin
VDD	Vitamin D deficiency
VDI	Vitamin D Insufficiency
VDN	normal vitamin D
WHO	World Health Organization
25 (OH) D	25 hydroxy vitamin D
1, 25 (OH)2 D	1,25 dihydroxy vitamin D

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KEYWORD**:** Serum 25 (OH) D, eGFR, HIV-infected adults, Thailand, Kidney Function Decline, Low vitamin D

Win Hlaing Than: KIDNEY FUNCTION DECLINE AMONG HIV-INFECTED THAI ADULTS: ROLE OF VITAMIN D AND OTHER CONTRIBUTING FACTORS. Advisor: Asst. Prof. OPASS PUTCHAROEN

Background: Each respective prevalence of hypovitaminosis D and Chronic Kidney Diseases (CKD) is high among Thai HIV-infected adults. Therefore, we examined the factors, including hypovitaminosis D, associated with kidney function decline among chronically treated HIV-infected Thai adults.

Methods: We analyzed participants, who were on suppressive combination antiretroviral therapy (ART) from the HIV-NAT long-term cohort, with estimated Glomerular filtration rate(eGFR) measured at least twice a year. Baseline were defined as when participants had a serum 25 (OH)D measured, with eGFR (>60 ml/min/1.73m^2 by CKD-EPI equations). The primary outcome was kidney function assessment in terms of eGFR decline.

Results: A total of 435 participants was observed through median follow-up of 30 (12 – 54) months. Median age was 44.4 (37.5-53.2) years old. Median serum 25(OH)D was 22.35 (17.5-28.4) ng/ml. Median baseline eGFR was 96.5(83.6-106.4) ml/min/1.73m^2, and 50% and 29% of participants were vitamin D insufficient and deficient respectively. GEE model showed coefficients of study factors on eGFR decline as follows: Low vitamin D -0.03 (95%CI: -3.28, 3.23) *p* 0.988; Follow-up in months -0.07 (95%CI: -0.09, -0.04) *p*< 0.001; age in years -0.20 (95%CI: -0.40, -0.01) P 0.042; being female 1.83 (95%CI: -0.79, 4.45) *p* 0.172 ;BMI -0.05 (95%CI: -0.37, 0.26) *p* 0.750 ;baseline eGFR 0.77 (95%CI: 0.67, 0.87) *p*<0.001; baseline HIV-RNA (log 10 copies/ml) -1.87 (95%CI: -4.47, 0.74) *p* 0.161 ; diabetes mellitus -1.98 (95%CI: -5.72, 1.77) *p* 0.301 ; hypertension -1.51 (95%CI: -4.38, 1.36) *p* 0.302; gout -2.19 (95%CI: -11.93, 7.54) *p* 0.659; co-infection with HBV -6.23 (95%CI: -13.28, 0.82) *p* 0.083; co-infection with HCV 5.68 (95%CI: -1.27, 12.62) *p* 0.109; previous exposure of PIs 0.08 (95%CI: -0.25, 0.41) *p* 0.632;current use of EFV2.87 (95%CI: 1.03, 4.70) *p* 0.002.

Conclusions: Among HIV-infected Thai adults, low vitamin D is not significantly associated with eGFR decline whereas age in years, follow-up duration in months, baseline eGFR, and current use of EFV were statistically significant. Further studies in larger populations with multi-ethnic groups are warranted.

Field of Study: Clinical Sciences Student‟s Signature……...

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##6074358630: วิชาเอก วิทยาศาสตร์การแพทย์คลินิก

คำสำคัญ: ระดับค่าวิตามินดีในเลือด, อัตราการกรองของไต, ผู้ใหญ่ติดเชื้อเอชไอวี, ประเทศไทย, การทำงานของไตลดลง, ระดับวิตามินดีต่ำ(KIDNEY FUNCTION DECLINE AMONG HIV-INFECTED THAI ADULTS: ROLE OF VITAMIN D AND OTHER CONTRIBUTING FACTORS) อ.ที่ปรึกษาหลัก : ผศ.นพ. โอภาส พุทธเจริญ

วิน เหลียง ธานห์:การทำงานของไตลดลงในกลุ่มผู้ใหญ่ไทยที่ติดเชื้อเอชไอวี: บทบาทของวิตามินดีและปัจจัยเสริมอื่น

ความเป็นมา: ทั้งภาวะวิตามินดีพร่องและโรคไตเรื้อรังมีความชุกสูงในผู้ใหญ่ไทยที่ติดเชื้อเอชไอวี ดังนั้น เราจึงศึกษาปัจจัย รวมถึงภาวะวิตามินดีพร่อง ที่สัมพันธ์กับการลดลงของการทำงานของไตในผู้ใหญ่ไทยที่ ติดเชื้อเอชไอวี

วิธีการศึกษา: เราวิเคราะห์ผู้เข้าร่วมการศึกษาซึ่งได้รับยาต้านไวรัสสูตรผสมจากโครงการศึกษาระยะยาว HIV-NAT ด้วยการประมาณอัตราการกรองของไต (eGFR) ที่วัดอย่างน้อยสองครั้งต่อปี จุดตั้งต้นเริ่มจากผู้ป่วยที่ วัดระดับวิตามินดี ในเลือดและมีอัตราการกรองของไต (eGFR) (มากกว่า 60 มล./นาที/1.73ตารางเมตร ด้วยสมการ CKD-EPI) ผลลัพธ์เบื้องต้นที่ได้คือการวัดการทำงานของไตในเทอมของอัตราการกรองของไต (eGFR)ที่ลดลง

ผลการศึกษา: ผู้เข้าร่วมการศึกษาทั้งสิ้น 435 คนได้รับการที่ได้รับการเฝ้าสังเกตในระยะยาวผ่านการติดตามสังเกตการณ์ ในระยะเวลาที่ค่ามัธยฐานของเวลาเท่ากับ 30 เดือน (12 – 54 เดือน) ค่ามัธยฐานของอายุผู้เข้าร่วม การศึกษา คือ 44.4 ปี (37.5-53.2) ค่ามัธยฐานของระดับวิตามินดีในเลือด คือ 22.35 (17.5-28.4) ng/ml ค่ามัธยฐานของอัตราการกรองของไต คือ 96.5(83.6-106.4) มล./นาที/1.73ตารางเมตร ร้อยละ 50 และ 29 ของผู้เข้าร่วมการศึกษา มีภาวะพร่องวิตามินดีและภาวะขาดวิตามินดี ตามลำดับ โมเดล GEE แสดงค่าสัมประสิทธิ์ของตัวแปรที่ศึกษาต่อการลดลงของอัตราการกรองของไต ดังนี้ ระดับวิตามินดีต่ำ -0.03 (95%CI: -3.28, 3.23) *p* 0.988 การติดตาม (เดือน) - 0.07 (95%CI: -0.09, -0.04) *p*< 0.001; อายุ (ปี) -0.20 (95%CI: -0.40, -0.01) *p* 0.042 เพศหญิง 1.83 (95%CI: -0.79, 4.45) *p* 0.172 ; ดัชนีมวลกาย -0.05 (95%CI: -0.37, 0.26) *p* 0.750 ; อัตราการกรองของไตที่ฐาน 0.77 (95%CI: 0.67, 0.87) *p*<0.001; HIV-RNA ที่ฐาน (log 10 copies/ml) -1.87 (95%CI: -4.47, 0.74) *p*0.161; เบาหวาน -1.98 (95%CI: -5.72, 1.77) *p* 0.301 ; ความดันโลหิตสูง -1.51 (95%CI: -4.38, 1.36) *p* 0.302; เกาต์ -2.19 (95%CI: -11.93, 7.54) *p* 0.659; การติดเชื้อ ตับอักเสบบีร่วมด้วย -6.23 (95%CI: -13.28, 0.82) *p* 0.083; การติดเชื้อตับอักเสบซีร่วมด้วย 5.68 (95%CI: -1.27, 12.62) *p* 0.109; การใช้ PIs มาก่อน 0.08 (95%CI: -0.25, 0.41) *p* 0.632; การใช้ EFV ในปัจจุบัน 2.87 (95%CI: 1.03, 4.70) *p* 0.002

สรุป: ในกลุ่มผู้ใหญ่ไทยที่ติดเชื้อเอชไอวี

วิตามินดีต่ำไม่มีความสัมพันธ์อย่างมีนัยสำคัญกับการลดลงของอัตราการกรองของไต แต่ อายุ (ปี) ระยะเวลาติดตาม (เดือน) อัตราการกรองของไตที่ฐาน เบาหวาน การใช้ **EFV** ในปัจจุบัน ผลอย่างมีนัยสำคัญทางสถิติ ต่อการลดล งของอัตราการกรองของไต การศึกษาต่อไปควรศึกษาในประชากรขนาดใหญ่ที่มีกลุ่มหลายเชื้อชาติ

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CHAPTER 1
Introduction

1.1 Background and Rationale

Many evidences pointed out that vitamin D plays important roles in a range of physiological functions and disease processes beyond its known role in bone metabolism. The role of body vitamin D level in patients with chronic systemic diseases have become a more interesting issue for well- understanding of its pathophysiological involvement in the diseases. Many emerging studies show that vitamin D deficiency is a pertaining factor to disease processes affecting cardiovascular health, bone and endocrine, diabetes and metabolic and renal aspects. [1-3] However, most studies have been done for general population and still few for HIV specific population.

It is found out that lower levels of serum 25(OH) D have been linked with reduced renal function or increased urine albumin, a marker of renal damage within general population during recent years. [4-6] However, for HIV population, it had been proved only in few western cohorts with several limitations in the context. [6, 7] Then, more new studies are required for HIV populations of different regions world-wide to prove this finding universally.

Based on previous studies, vitamin D deficiencies take place among 21% (95%CI: 17%, 25%,) of adolescents of HIV population in Thailand [8]while it occurs 58% in general population of South East Asia during 2010s. [9] In United States, it has occurred up to 40% of general population & 30% of HIV population in 2011. [10,11]

Per 2017 data, in Thai general population, prevalence of CKD stage 3 and 4–5 was 33.2 and 4.3%, respectively. Prevalence of CKD stage 3–5 in hypertensive population was 37.5%. [12]

In Japanese HIV population as for Asian data in 2017, the prevalence of CKD was 18.6% for age 50–59, 28.5% for 60–69, and 47% for over 70. [13] As of 2011, Prevalence of early stages and advanced stages of CKD were 39% and 30%

among HIV adults in Thailand. So, HIV population are generally high risk of CKDs and kidney function decline.

In these days, highly active antiretroviral therapy (HAART) become advanced and the life span of HIV patients are longer and most become aging. So thus, prevalence of Non -AIDS morbidities including bone and kidney complications are increasing. [14] The long-term effects of anti-retroviral agents contribute these morbidities. Particularly, non-nucleoside reverse transcriptase inhibitors (NNRTIs), is one of the causes of low 25(OH) D in HIV patients.[15] HIV-infected people are also more vulnerable to fourfold risk of kidney diseases and a threefold risk of end-stage renal disease compared to HIV-uninfected people. [16,17] Based on these contextual facts, it is very wonderful should there is the relationship between vitamin D levels and kidney functions among HIV-infected adults. Moreover, the magnitude of the impacts of low vitamin D and kidney dysfunction are high not only in regions but also in the world particularly in HIV settings.

Hence, for specifically among HIV-infected Thai adults, it is very worthy to explore whether it is that the kidney function decline in HIV infected adults are due to low vitamin D or not.

1.2 Research Question

Is low vitamin D associated with kidney function decline among HIV-infected adults in Thailand?

1.3 Research Hypothesis

Low vitamin D is associated with kidney function decline among HIV-infected adults in Thailand

1.4 Keywords

Vitamin D deficiency (VDD)/Hypovitaminosis D, Low vitamin D, Kidney function Decline, eGFR decline, HIV adults, Thailand

CHAPTER 2
Literature Review

2.1 Vitamin D

2.1.1 Vitamin D and its pathophysiology

Vitamin D is a fat-soluble vitamin and a micronutrient traditionally known as which is required for bone and teeth health. Based on origins, D2 is obtained from plants. D3 is available naturally in only very few foods like some fatty fish, fish liver oils, and eggs from fed hen and several fortified foods in some countries with specific regulations. However, vitamin D_3 (cholecalciferol), an active form, which have hormonal effects can be formed in the human skin by exposure to the UV light of the sun as de-novo synthesis. If the photo-conversion in the skin is not enough because of decreased sun exposure (e.g., in cold seasons like winter, autumn), intake of adequate vitamin D from the diet is absolutely fundamental. According to geographic location or food availability, adequate vitamin D intake might be insufficient on a global scale.

Normal recommendation for a healthy adult is 800 IU daily as supplements. Vitamin D excess is termed as hypervitaminosis D and vitamin D deficiency is termed as hypovitaminosis D. Both these conditions are abnormal. However, deficiency is more prevalent than excess. Vitamin D deficiency causes rickets in children and osteomalacia in adults. If severe in elderly patients, osteoporosis will occur.

Nowadays, the roles of vitamin D playing in body mechanisms had been discovered more in various organs and systems. In this study, the effect of vitamin D on kidney functions were explored among HIV-infected adults in Thailand.

2.1.2 Serology of Vitamin D

Vitamin D3 has two important forms as serological tools in research. They are serum 25 (OH) D and serum 1, 25 (OH) 2D. Serum 1, 25 (OH) 2D is the active form but less stable than serum 25 (OH) D. However, the active form is directly influenced by several factors. [18, 19]

Serum 25 (OH) D is a tool of objective measurement for vitamin D deficiencies. According to International Endocrine Society, Vitamin D Deficiency (VDD) is operationally defined as serum 25 (OH) D level below 20ng/ml; Vitamin D Insufficiency (VDI) as serum 25 (OH) D level between 20 and 29.9ng/ml; Vitamin D Normal (VDN) as serum 25 (OH) D level 30ng/ml and above respectively. [20]

Based on physiology, serum 25 (OH) D is obtained after hydroxylation in the liver and serum 1, 25 (OH) 2 D is formed after second time hydroxylation in the kidneys. Therefore, in patients with kidney diseases will surely have low level of serum 1, 25 (OH) 2 D. So, there is a binary relationship between 1, 25 (OH) 2 D and kidney function. [21]

2.1.3 Causes of Low Vitamin D

There are well-known traditional factors causing hypovitaminosis D. They are female sex, dark skin pigmentation, high BMI, physical inactivity, reduced sun exposure, and winter season. Dietary causes such as lack of vitamin D in foods or absorption defects of gastrointestinal tract, liver and renal problems which are the organs for sites of de-novo synthesis of vitamin D will also contribute this condition. Moreover, seasonal and geographical effects are also influencing factors.

Specific contributing factors in HIV population are advanced stage of disease, exposure to certain antiretroviral drugs like Efavirenz, Tenofovir and Ritonavir-boosted protease inhibitors, and immune activation. Other considerable factors are co-infections with HBV and/or HCV.

2.1.4 Vitamin D in HIV perspectives

Vitamin D has also independent actions of producing high inflammatory cells and anti-infective properties in HIV patients. However, higher than optimal level of serum 25 (OH) D may be associated with immune dysregulation by relating with higher levels of pro-inflammatory cytokines especially in older HIV patients. [22]

Vitamin D deficiency is an independent risk factors for cardiovascular diseases and metabolic disorders like insulin resistance and type 2 diabetes mellitus.[2] EACS guidelines recommend for monitor hypovitaminosis D in every HIV patients

having risks of low vitamin D. Vitamin D repletion is also advised to those till the normal serum 25 (OH) D as of IES criteria is achieved. [23]

One-month supplementation of vitamin D can also modulate disease relevant T-cell functions in HIV infected patients, evident by a UK clinical trial in 2015. This reflects vitamin D also has anti-infective properties. [24]

HBV-HIV co-infected female patients on ART are more prone to hypovitaminosis D. [25]

Among patients with HIV and HCV co-infections, hypovitaminosis D may worsen liver fibrosis calling for adjuvant vitamin D supplementations. HIV infection, Fib4 Score>1.45 and low vitamin D are strong independent factors for advanced fibrosis. [26]

Lower level of 25 (OH) D has also been associated with lower bone mineral density and higher risk of heart failure, coronary heart disease, and diabetes in whites and not in blacks as in general population. [27, 28]

Regarding bone health, HIV itself causes a lot of complications affecting on parathyroid hormones and bone mineral density, eventually leading to osteopenia. High clinical staging (WHO stage 4) before ART shows highly the relationship with osteopenia. [30]

Followings are few big studies about vitamin D in HIV settings. [3] Hauge et al proved that there is lower serum level of 1, 25 (OH) 2 D in symptomatic HIV patients if compared to asymptomatic HIV patients. And there is the relationship between lower serum level of 1, 25 (OH) 2 D and shorter survival times. One cohort from Tananzia concluded that lower serum 25 (OH) D cause more rapid progression of HIV staging and higher mortality. Sudfeld et al. also showed that VDD may progress to a high mortality in those on ART and this relationship is independent of impaired T cell reconstitution. In follow-up of EuroSIDA, VDD is independently associated with increased mortality and more prevalence of AIDS defining conditions.

2.2 Chronic Kidney Diseases (CKD)

2.2.1 Kidney Function and its indicators

There are several functions of the kidneys. Among them, urinary excretions for toxins and metabolites for clearance are mainly referred in this study. Based on anatomical units, there are glomerular functions and tubular functions.

As indicators, GFR (glomerular filtration rate) is for glomerular function and urine albumin, urinary phosphorus were for tubular functions markers, respectively.

2.2.2 Types of kidney damage and indicators

Basically, there are two types of kidney damage-structural and functional. Structural damage can be known by an elevation in urinary protein excretion or proteinuria (albuminuria). Glomerular filtration (GFR) < 60 ml/min generally reflects the functional damage of glomerular portions of nephrons. Other tubular markers like urinary calcium, urinary phosphorus levels, and urinary albumin to globulin ratios indicate tubular malfunctions. Some patients may have both indicators showing both structural and functional damage in chronic cases. Generally, estimated glomerular filtration rate (eGFR) is a conventional surrogate indicator for most of the cases.

2.2.3 Estimated Glomerular Filtration Rate (eGFR)

There are several equations to calculate eGFR based on ethnicity, gender, age and types of clearance of metabolites from the kidneys. [31] Among them, a very basic one is looking for rate of clearance of serum creatinine. However, serum creatinine does not vary linearly with GFR and affected by age and sex and muscle mass. So, there are equations with adjustments differences in muscle mass using age, sex, (weight) coefficients to estimate GFR better. Different equations are used in different populations. For Thai population, MDRD equation with Thai racial correction factor can give the most accurate estimate value of kidney function. [31] However, Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) is still the conventional one not only for international population but also for Thai population according to 2015 nephrology guidelines of Thailand. [32] It is as follows:

141 × min (Scr/**K**, 1) **α** × max (Scr/**K**, 1)-1.209 ×0.993Age × 1.018 [if female]

Where κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

2.2.4 Diagnosis of Chronic Kidney Diseases

CKD has been defined as kidney damage or reduced kidney function that persists for more than three months. This means the duration makes the diagnosis whether it is structural or functional damage. [52]

2.2.5 Causes of Chronic Kidney Diseases or kidney function decline

There are traditional and HIV factors. Traditionally high-risk groups include individuals with diabetes, hypertension or with family history of kidney failure, heavier body weight, lesser physical activities, old age, or individual if one is an African, Americans, Hispanics, Pacific Islanders, American Indians or black people. Co-infections like HCV or CMV also contribute to this condition.

Underlying local pathologies affecting glomerular, tubulo-interstitial, vascular functions (Host & Disease factors) which are categorized as inflammation, inherited, mal-formation, lupus, obstruction and infection causes are also the precipitating factors.

Specific HIV factors are advanced HIV itself, HIV spectrum of kidney diseases, nephrotoxic antiretroviral drugs (ARVs) like Tenofovir, Indinavir, Atazanavir, CD4 counts before and after ARVs, viral load before and after ARVs.

Some common factors for Thai population are age, gender, diabetes, hypertension, hyperuricemia, history of kidney stones and use of traditional medicines.

Stage	Description	GFR (ml/min/1.73m^2)
T	At risk	> 90 (with risk factors for CKD)
1	Kidney damage (proteinuria +) normal GFR	>90
2	Kidney damage (Proteinuria +) mild decrease GFR	60-89
3	Moderate Decrease GFR	30-59
4	Severe Decrease GFR	15-29
5	End-Stage Kidney	<15 or dialysis

Table A. Staging of chronic kidney diseases (based on eGFR)

2.2.6 Kidney Functions in HIV perspectives

CKD prevalence was 13% and 0.5% reached to end stage renal disease (ESRD) among HIV adults in Japan in 2017. [13]

The burden of kidney complications are due to overall increase in life expectancy and aging of the HIV patients. Then metabolic complications become predominant in these days. [33] Since 2009, CKD prevalence was at 17% which were contributed by the same factors in UK. [34]The obvious racial variation is that blacks

are at high risk of progression to ESRD unless receiving HAART. [35] In other words, black skin owners are more vulnerable to faster decline of kidney function.

HIV infected persons continue to lose kidney functions in spite of successful ART due to therapeutics, intermittent viraemia, and particularly traditional risk factors. [36]

Traditional risk factors play more important than HIV factors because epidemiology of HIV related kidney disease was drastically decreased in the ARV era today. During pre-ART era, HIV associated nephropathy (HIV AN) was the commonest form of HIV related kidney diseases. [37]

HIV factors have lesser impacts than traditional ones. Because of ART, renal complications due to HIV, HIV kidney disease spectrum might be well-controlled. However, the renal impact arising from ARVs become issues. [37]

The well-known ARVs which has side effects on kidneys and its functions are Efavirenz, TDF [38], Atazanavir [39], Indinavir. Other newer agents may also have impacts on kidneys.

Overall duration of ART has impact on kidney function decline but duration of TDF exposure are not so significant. However, TAF is better for choice as it has less adverse effects on bone and renal aspects in these days. [38]

2.3 Vitamin D and Kidney Function Association

2.3.1 in General population

Black people generally have lower 25-hydroxyvitamin D levels experiencing a disproportionate burden of ESRD if compared with white individuals. 20-year CKD incidence was higher among African Americans than whites, a difference that is explained in part by albuminuria. [40]

Observational studies have shown that higher 25 (OH) D levels are associated with lower risk of kidney function decline or albuminuria in general population. Randomized clinical trials have proved that supplementation of 1, 25 (OH) 2 D or its analog could reduce albuminuria in patients with CKD. However, whether reduction of proteinuria can save kidney function is unclear yet. [41]

2.3.2 in HIV population

Tin et al, an US multicenter HIV cohort showed that white older people with comorbidities showed the significant association between low 25 (OH) D and rapid eGFR decline. However, younger black people who had higher eGFR than whites in the cohort did not prove this association statistically significant. Regarding serum 1, 25 (OH) 2 D, both shows with rapid decline of eGFR but not statistically significant.

Hence, their findings were quite so challenging to conclude. One reason was that it was against that black persons had faster eGFR decline. Another reason was the study include HIV men only. Even though the cohort was multi-center approach, it had unequal distributions of age and eGFR. The other minor drawback was being also a sub-study of the main cohort so thus it might had had statistical limitations against contextualization. The association between Lower serum 25 (OH) D and rapid eGFR decline among white Americans were explained by the possibility of the effect of early manifestation of end organ disease related with the accelerated aging in HIV patients on ART. [42]

Table B. HIV spectrum of kidney diseases

HIV-associated nephropathy (HIVAN)
Immune complex-mediated kidney diseases
HIV immune complex kidney disease (HIVICK)
Membranoproliferative glomerulonephritis, with or without HCV co-infection
Membranous nephropathy, with or without HBV co-infection
IgA Nephropathy
Non-collapsing focal segmental glomerulosclerosis
Minimal change disease
Arterionephrosclerosis
Diabetic Nephropathy

Table C. Literature Review in Brief

Author, Year	Research	Findings
de Boer IH, et al (2011) Clin J Am Soc Nephro	Serum 25-hydroxyvitamin D and change in estimated glomerular filtration rate	25% higher risk of rapid eGFR decline by every lower 10 ng/ml of serum 25 (OH)D; magnitude of association was higher among patients with diabetes
Damasiewicz MJ, et al (2013) Am J Kidney Dis	Serum 25-hydroxyvitamin D deficiency and the 5-year incidence of CKD	In general population, significantly associated with albuminuria only
Tin A, et al (2017) AIDS Res Hum Retroviruses	Vitamin D Status and Kidney Function Decline in HIV-Infected Men: A Longitudinal Study in the Multicenter AIDS Cohort Study	Low serum 25 (OH)D was associated with eGFR decline among white Americans significantly (older with co-morbidities and lesser baseline eGFR)
Zhang L, Tin A, et al (2017) AIDS Res Hum Retroviruses	Vitamin D Deficiency and Metabolism in HIV-Infected and HIV-Uninfected Men in the Multicenter AIDS Cohort Study	Black race was associated with higher levels of 1,25[OH]2D; levels of 1,25[OH]2D and 25[OH]D positively correlated in HIV-infected men.

CHAPTER 3
Objectives of the Study

3.1 Primary objective

To examine the relationship between low vitamin D (vitamin D insufficiency and/ or vitamin D deficiency) and kidney function decline among HIV infected adults in Thailand

3.2 Secondary objectives

1. To compare the characteristics among the different groups of vitamin D level of HIV-infected adults in Thailand

2. To identify the significant contributing factors to kidney function decline among HIV-infected adults in Thailand

CHAPTER 4
Research Methods

4.1 Methodology

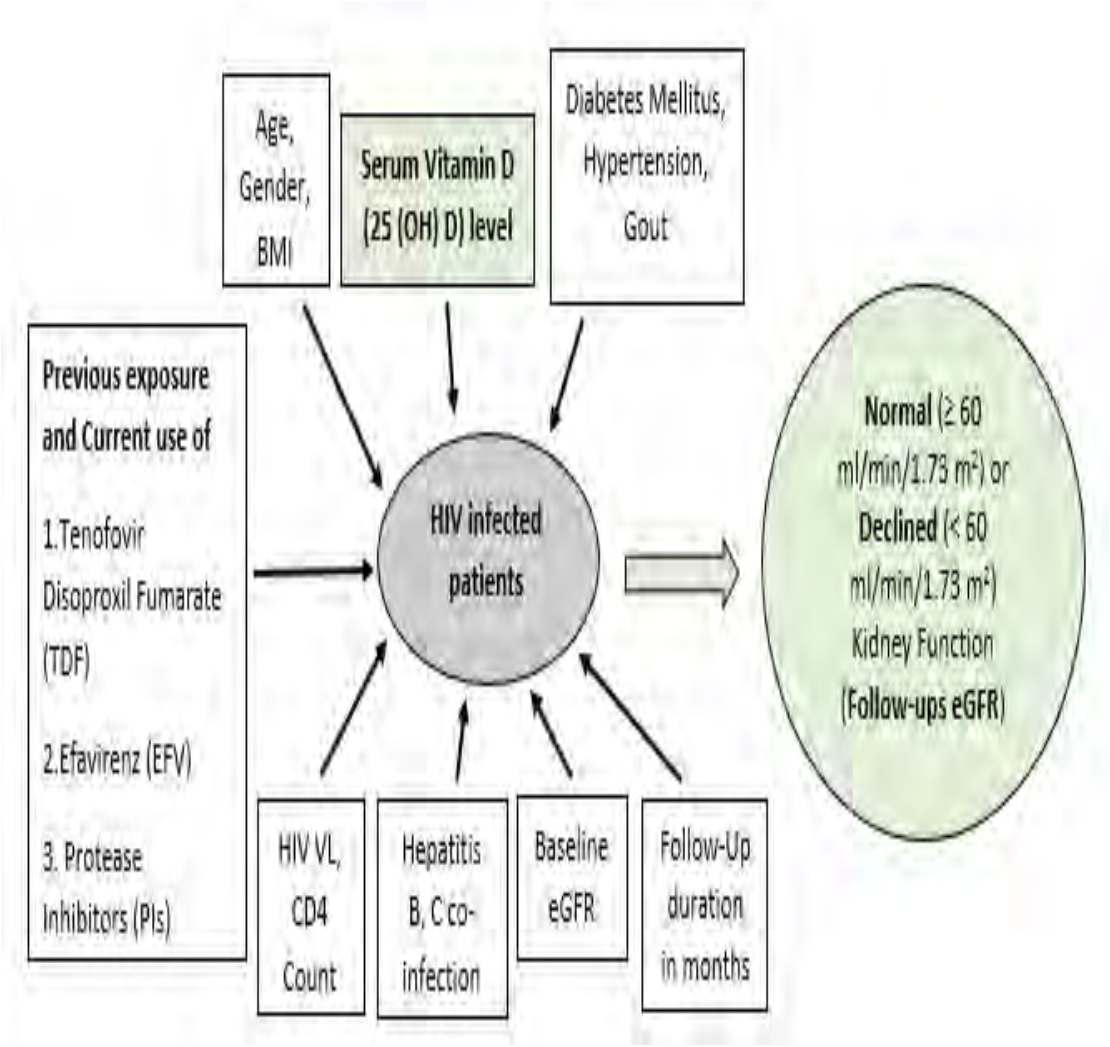

Figure (1) Conceptual Framework

The study was conducted among HIV-infected adults in Thailand to observe longitudinally follow-ups of eGFR level as outcomes. We tested a lot of variables in the study as shown in figure (1). The key predictor we tested was serum vitamin D 25 (OH) D level to examine the relationship between serum 25 (OH) D and follow-up eGFR outcomes. Other adjusted covariates were biological factors like age, sex and BMI, comorbidities like diabetes mellitus, hypertension and gout, co-infections with

hepatitis B virus (HBV) or hepatitis C virus (HCV), HIV parameters like HIV RNA level, CD4 count, baseline eGFR and follow-up duration in months and common antiretroviral drugs (ARVs).

4.2 Operational Definitions

1. Age of the participants

-Age of the participants was defined as age at the time of baseline serum 25 (OH)D and eGFR as taken.

-Age was an inclusion criterion of the participants. Participants of this study completed 18 at baseline.

2. Sex

-Both HIV-infected men and HIV-infected women were included.

3. Vitamin D levels

-"Low vitamin D" in the primary objective of the study includes vitamin D deficiency and vitamin D insufficiency which were operationally defined according to International Endocrine Society.

-Vitamin D Deficiency (VDD) was operationally defined as serum 25 (OH) D level below 20ng/ml; Vitamin D Insufficiency (VDI) as serum 25 (OH) D level between 20 and 29.9ng/ml; Vitamin D Normal (VDN) as serum 25 (OH) D level 30ng/ml and above respectively.

-Serum 25 OHD level of every participants was the key predictor which was also baseline in one time-point.

4. Kidney Function Decline

- The kidney function decline in the primary objective was defined by all levels of changes of estimated Glomerular Filtration Rate (eGFR) in any degree longitudinally throughout the study.

- eGFR were calculated by Chronic Kidney Disease-Epidemiology Collaboration Creatinine (CKD-EPI) equation based on serum creatinine level. (For equation, please see in literature review.)

5. Baseline

- Baseline was defined as the starting time-point of this study for all participants. However, according to the dataset, different participants had different real-time baseline.

- Baseline was the starting point when participants had serum 25 (OH) D and accompanying eGFR at the same time in the cohort.

6. Follow-up

- Follow-up was operationally defined as all the serial or consecutive visits after the baseline every six-monthly interval. However, it was measured in terms of months.

7. Hypertension

- This was a covariate of the study for a co-morbidity of participants because this is a theoretical factor having impacts on kidney function.

-Hypertension was operationally defined as by means of clinical definition (systolic BP>130mmHg and/ or diastolic BP>90 mmHg) at baseline and /or hypertension which was already diagnosed before baseline.

8. Diabetes Mellitus

- This was also a covariate of the study for a co-morbidity of participants because this is a theoretical factor having impacts on kidney function.

-Diabetes mellitus was operationally defined as by means of clinical definition (fasting serum glucose> or =126 mg/dl) and/ or already diagnosed before baseline.

9. Hepatitis B virus (HBV) co-infection

- This was also a covariate of the study as a co-infection of participants because this is a theoretical factor having impacts on vitamin D level and kidney function.

- HBV co-infection was operationally defined as clinical definition (Hepatitis B virus surface antigen- HBs Ag positive) at baseline and/ or already diagnosed before baseline.

10. Hepatitis C virus (HCV) co-infection

- This was also a covariate of the study as a co-infection of participants because this is a theoretical factor having impacts on kidney function.

- HCV co-infection was operationally defined as clinical definition (antibodies to Hepatitis C virus- anti HCV Ab positive) at baseline and/ or already diagnosed before baseline.

11. Antiretroviral drugs (ARVs)

- These were also covariates of the study because they are the well-known theoretical factors having impacts on vitamin D level and/or kidney function.

-The study included Tenofovir Disoproxil Fumarate (TDF), Efavirenz (EFV) and Protease inhibitors (PIs). All PIs were grouped as drug-class, PI.

-Previous exposure were measured in terms of years; and current use were defined as presence or absence. Previous exposure and current use were defined as before and after the baseline of the study.

12. HIV parameters

- HIV parameters were Viral load (VL), CD4 count, CD4% and CDC staging at baseline. CD4 nadir were also assessed.

-Post ARV measure but before baseline were inclusion criteria of the study, the salient one was that all participants were virologically well-suppressed VL<400 copies/ml over last six months from baseline after on ARV. This inclusion criteria select the participants to exclude the sampling errors of confounding effects of HIV on vitamin D level and/ or Kidney function.

14. Duration of ARVs

- Duration of ARVs in this study may differ from actual duration of ARVs because the study will emphasize the impact of vitamin D level.

- So, in this study, previous exposure of ARVs is operationally defined as from the time of commencement of ART to the time of baseline serum 25 (OH)D test. Current use was defined as presence or absence along the follow-up duration in months.

15. Adjusted factors

- These were also factors influencing vitamin D and/or kidney function. They were not considered as covariates but adjusted to get the same ground or baseline to exclude confounding effects.

- They are dark skin, seasonal variation for vitamin D aspects. These were obtained by deriving adjusted data from the main cohort HIV-NAT 114. Age and sex- adjusted eGFR were also used in the study.

- Body mass index (BMI) variable in exchange of physical inactivity will also be included.

16. Confounders

-Theoretical factors influencing vitamin D and/or kidney function are considered as covariates to look for any their effect modification (interaction) to the study. The other conditions apart from them which may have confounding effects are HIV ART defaulters due to poor compliance or missing pills and patients with concurrent medications. They were excluded anyway for the statistical simplification and clarification.

4.3 Study Design

Exploratory approach in an existing local HIV sub-study, HIV-NAT 114 with retrospective analyses were conducted in longitudinal observation. In retrospective cohort, the study looked for the association between serum 25 (OH) D and eGFR at baseline and serial changes of eGFR during each six-month interval follow-ups longitudinally. The salient reason here we used cohort rather than clinical trial was because of feasibility of resources and data in our historical cohort. Another reason was to solve ethical consideration of vitamin D supplements which might affect our

study results. Thus, retrospective study is more feasible. The study explored mean eGFR differences of low vitamin D for eGFR decline.

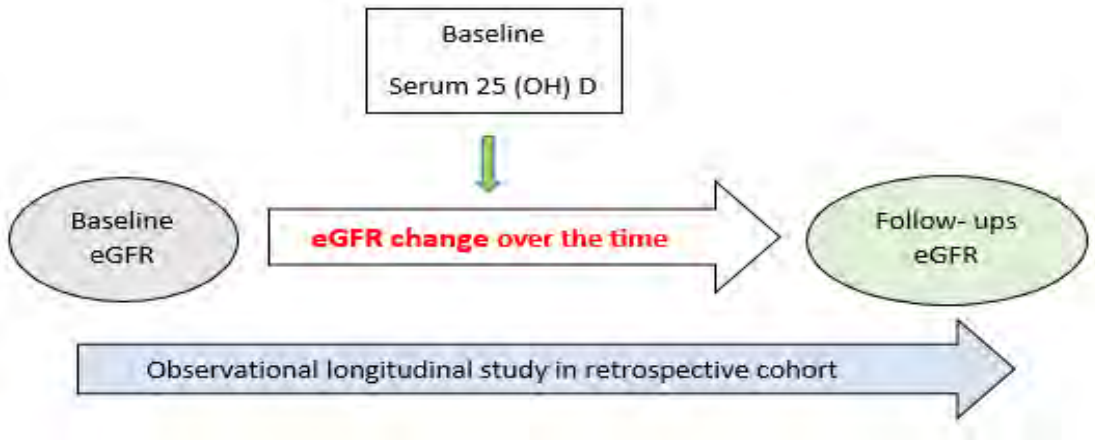

Figure (2) Study Design

4.4 Sampling

4.4.1 Approach to participants

1.Population

We observed retrospectively among HIV-infected adults from HIV-NAT 114 cohort who were on ART and virologically suppressed at least for 6 months with serum 25 (OH) D and eGFR level above 60 ml/min at baseline. Participants with every 6-month eGFR were recruited in this study.

2.Study Cohort

HIV-NAT 114 cohort is a local HIV one assessing the incidence and predictors of TDF associated nephrotoxicity and pharmacokinetics of TDF in HIV-1 infected Thai patients (HIV-NAT 114); Glomerular filtration rate, HIV-infected Thai patient, serum creatinine, cystacin C, creatinine clearance (HIV-NAT 114.1), Mechanism and clinical significance of hypophosphatemia in HIV-infected patient receiving antiretroviral therapy (HIV-NAT 114.2).

3.Study Sites

Study sites were the HIV- Netherlands Australia Thailand Research Collaboration (HIV-NAT), Thai Red Cross AIDS Research Center, and King Chulalongkorn Memorial Hospital which all are situated in Bangkok where belongs to the tropical climate and geography.

4.Study Period

Our current study included all previously collected data from September,1996 to July,2018 throughout these cohorts.

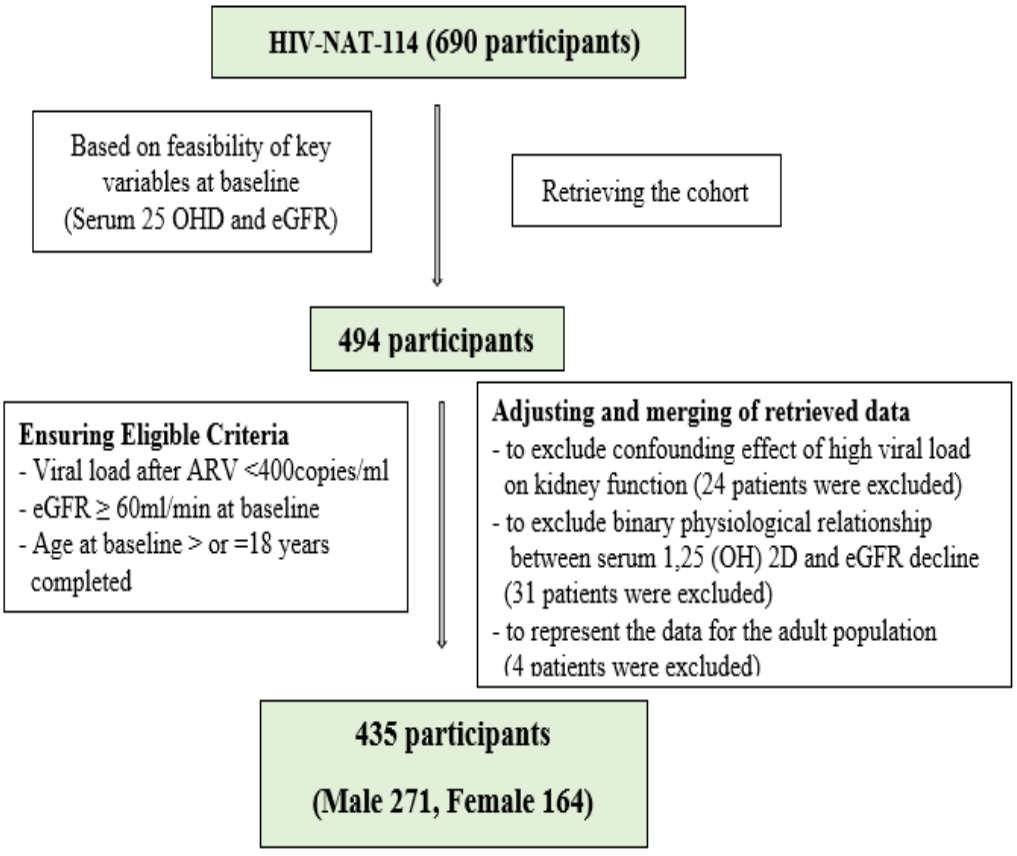

Figure (3) Approach to participants

4.4.2 Eligibility criteria

Inclusion criteria included

HIV -infected adults who completed 18 at baseline and who was virologically suppressed (plasma HIV1 RNA<400 copies/ml within the past 6 months from baseline who was treated on ART.

Exclusion criteria included

-Patients with other renal diseases which may have confounding effect on eGFR level (already diagnosed before baseline or by USG kidney and eGFR tests at baseline);

-Patients with HIV spectrum of renal diseases (Table B) to avoid confounding kidney function decline (already diagnosed before baseline or by USG kidney and eGFR tests at baseline);

-Patients with pre-existing bone diseases to avoid confounding vitamin D level variation (already diagnosed before baseline or by DXA profiles at baseline);

-Patients with metabolic diseases which may confound vitamin D metabolism in kidneys and liver (already diagnosed before baseline or by USG Abdomen and serological tests for lipids, liver and hormones, especially PTH at baseline);

-Patients with endocrine diseases which may have the interaction with vitamin D metabolism (already diagnosed before baseline or by USG Abdomen and serological tests hormones, especially PTH at baseline);

-Patients with other well-known confounding factors of CKD (already diagnosed before baseline or by clinical serology, virology and immunology);

-Patients with other well-known confounding factors of vitamin D deficiency (already diagnosed before baseline or by clinical serology, virology, and immunology);

-Patients on other drugs apart from ARVs causing impaired renal functions (known by medical history);

-Patients on other drugs apart from ARVs causing vitamin D level variations (known by medical history).

4.5 Ethical considerations

The enrolled patients in this study were a portion of HIV-NAT cohort 114. All the existing data were de-identified and were used in the study only for research purpose, fulfilling the criteria of patients‟ dignity and their confidentiality in regards of respect for person. So, there was no harm to the patients at all. There was also a clear criterion for inclusion and exclusion of patients. In other words, an absolute criterion for the selection process of patients. This could answer the criteria of Justice. For Beneficence and Non-Maleficence, this study contributed not only the clinical impact on individuals but also to the HIV population for the more understanding of the diseases and complications. This study was able to update to the research and academic, promoting clinical improvement of HIV community as well. The study was thoroughly ensured by methodology for the ethical issues of vitamin D supplementation without objection. But not limited to ethical considerations, the project protocol also followed stipulation of local regulations. And the research was conducted in accordance with GCP guidelines and the declarations of Helsinki. The project was carried out under the approved access to data source of primary organization HIV-NAT. The project was submitted to the Institutional Review Board on Human Research at the Faculty of Medicine, Chulalongkorn University for the ethics approval (IRB 037/62). It was approved on March 5,2019 under Certificate of approval 252/2019.

4.6 Informed Consent

Because this is the sub-study of the existing cohort and all existing data were used for research and academic purposes only, which are also de-identified in nature in regards of patient confidentiality. There is also no harm to the patients. Hence, there would be no informed consent from the patients. However, the permission to

study and explore the cohort is already obtained formally from the authority of the HIV-NAT organization.

4.7 Data collection

4.7.1 Variables

Predictors were serum 25(OH) D at baseline while outcome variables are eGFR measures baseline and during follow-ups. Other variables included in the study were as follows.

Baseline variables were eGFR and HIV-RNA. Time factor was duration of follow-up (months). Biological variables were age, sex and BMI. Co-morbidities and co-infections were hypertension, diabetes mellitus, gout, hepatitis B virus (HBV), and hepatitis C virus (HCV). ARVs were Tenofovir Disoproxil Fumarate (TDF), efavirenz (EFV), and protease inhibitors (PIs) in terms of previous exposure (in years) and current use (presence/absence); where previous exposure and current use were demarcated as before and after the baseline of the study.

4.7.2 Materials and Methods at main cohort

The laboratory measures were retrieved as previous collected data from HIV-NAT 114. As for laboratory procedures of HIV-NAT 114, they were as follows.

Blood was drawn after 10 hours of fasting to assess CD4 count, HIV-RNA, fasting serum glucose, serum creatinine, 25(OH) D levels, and HBV profile including HBs Ag. Informed consent were obtained from all participants in the relevant cohort. [44]

The drawn fasted whole blood was centrifuged at 2500 rpm for 20 minutes and plasma was stored at -80℃ until testing. Serum 25-(OH)D were tested in by the Architect Chemiluminescent microparticle immunoassay (CMIA; Abbott, Barcelona, Spain).

Plasma HIV 1 RNA, HBV DNA & HCV RNA viral loads were checked by real-time Polymerase Chain Reaction assay (Abbott Molecular Inc. Des Plaines, IL, USA)

Tests for anti-HIV body, CD4 lymphocyte count, anti- HBV antibodies like anti HBs, anti HBe, anti HBc, anti-HCV antibody were repeated using

chemiluminescent microparticle immunoassay (CMIA) (Abbott test generation3, Abbott Architect ci4100, Wiesbaden, Germany).

The modified Jaffe method was used for measurement of serum creatinine level.[45] Diabetes Mellitus was defined by fasting serum glucose≥126 mg/dl.

Bone mineral density of Thoracic and Lumbar spines were measured by Dual Energy X-ray absorptiometry technique (Lunar; General Electric Healthcare, Madison, Wisconsin, USA). The scans were analyzed using enCORE software version14.1 (enCORE; General Electric Healthcare, Madison, Wisconsin, USA). BMD Z-scores comparing the absolute BMD results of participants to the average results of Thai reference of the same age and sex were calculated.

Body composition was checked with bioimpedance analysis BIA using Body Composition Analyzer (In Body S20, Biospace, Korea) where skeletal muscle mass, body fat mass, and total body water were analyzed. Body weight, height, and blood pressure were also noted.

4.8 Sample Size Determination

As the approach of this study was on exploratory in an existing cohort, an informal calculation was more appropriate for sample size estimation. Since this study contained single baseline measures of the two samples (arms) of low and normal vitamin D groups, the following „two sample independent t test equation" was used for serial continuous outcomes of eGFR.

$$N = \frac{2 \times (Z_{(1-\alpha/2)} + Z_{\beta})^2 \times \sigma^2}{\delta^2}$$

Where N= number of participants in each group, Z2α=1.96 at 5%significant level, Z2β= 0.842 at 80% power, σ=standard deviation, δ= clinical significance between the group we would like to detect

The study was assumed in the format of a continuous response variable from independent control and experimental subjects with 1 control(s) per experimental

subject. To evaluate the eGFR change by Vitamin D status at baseline (Low or Normal) and CKD grade at baseline in a multivariate model, our study based the sample size on the paper by Tin et al _'Lower 25(OH) D levels in white participants were associated with faster eGFR decline (in Caucasians). There only have the predicted annual changes in eGFR after dividing the vitamin D levels into tertiles and the odds („risk‟) of going from CKD stage 1-2 is the same as going from 3-4 and the same as going from 4-5.‟For 2 years of follow-ups, it would expect to see the eGFR in the vitamin D deficient group decrease by 3.44 units (SD 2.15) and in Vitamin D insufficient group we would expect to see it decrease by 2.86 units (SD 2.11) and with 213 sufficient and insufficient patients that would give us 80% power to detect this difference at a 2-sided significance level of 5%. In their study the response within each subject group was normally distributed with standard deviation 14.9 and difference in the experimental and control means was 4.05. Therefore, we assumed to recruit 213 experimental subjects and 213 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. So, the total sample size will be 426 participants.

By under this assumption, it made to get increasing power and a big reduction in sample size if there was an increase in number of follow-ups based on the linear mixed model results. Since several years of follow-ups (in our cohort) hence there have excellent power to look at this even with around 100 patients in the low and normal Vitamin D groups. As such, the resultant our sample size made the strong representation even with logistic regression which is the solution to normal distribution of the dataset. For feasibility and simplification, Generalized Estimating Equations were used in multivariate analysis over 435 participants retrieved from the cohort.

CHAPTER 5
Data Analyses

All statistical analyses were performed using STATA statistical software, version 14. Normality of the data set was checked by Shapiro-Wilk Normality Test**.** Summary statistics were presented by mean (SD) or median (IQR) for continuous variables and frequency count and percentage for categorical variables.

Patients characteristics were stratified by 25(OH)D levels (*<30ng/ml for low Vitamin D and ≥30ng/ml for normal Vitamin D)* for descriptive studies to compare the characteristics among the different groups of vitamin D level of HIV infected adults in Thailand. Comparison of variables was done by chi square tests (or Fisher extract test) for categorical variables and independent t tests (or Mann-Whitney U test) for continuous variables.

Then we did univariate analysis and multivariate analysis by Generalized estimating equations (GEEs) for repeated measures of follow-up eGFR as eGFR outcomes in longitudinal observation. Magnitude of association were calculated as mean eGFR differences and adjusted mean differences within 95%CI. Variables with P value <0.25 during univariate analyses were put in multivariate analysis where $P < 0.05$ was considered statistically significant.

Subgroup analyses were also done in multivariate models before ARV adjustments across the different BMI categories.

Since our study was a retrospective study with existing data, we had to do some data management. Different patients had taken tests on serum 25 (OH)D at different time-points in the cohort. We had to solve the issue by statistically assuming serum 25 (OH)D time-point and eGFR at the same time as baseline followed by consecutive six- month interval eGFR follow-ups. For the patients with more than one time of 25 (OH)D in the cohort,25 (OH) D with eGFR at the same time were taken as baseline. For patients with both 25 (OH)D had accompanied with eGFR tests, the earlier point of time in the cohort were taken as baseline. For every eGFR follow-ups of participants were six-month interval apart from own baseline of each participants, and for those with no follow-up eGFR at exact time-point, before & after three-month interval of eGFR were subsequently considered for the missing follow-up as merging timeframe format. All the duration in this study including age were calculated to and from the time-point of baseline unless specified otherwise.

In our study, seasonal adjusted values of serum 25(OH)D, age and sex adjusted eGFR were subsequently derived from HIV-NAT114. [43]. The reason why serum 25(OH) D was used as tool for assessment is to rule out prevalence of hypovitaminosis D due to CKDs i.e. to exclude the binary relationship between serum 1, 25 (OH) 2D and eGFR decline. Other reasons were because they were more stable form and relatively longer than 1,25 (OH) 2 D in serum. HAART were guided by DHHS/Kaiser Panel guideline and defined by 3 or more ARVs consisting of one or more PIs or one NNRTI or NRTI: Abacavir or Tenofovir disoproxil fumarate or an integrase strand transfer inhibitor or an entry inhibitor [50].

CHAPTER 6
Significance of the Study

Our study has several significances over other studies of kidney function, HIV setting studies, and vitamin D related studies.

Serum 25 (OH)D was used as vitamin D level because it is more objective as a tool of assessment for composite of vitamin D in serum derived by skin and liver and it is stable and longer half-life than serum1,25 (OH)2D[3].And it has no physiological relationship with eGFR unlike serum 1,25 (OH)2D.

eGFR which are conventional surrogate indicators were used as outcomes for kidney function decline and they were calculated by CKD-EPI equations which is conventional and suitable for Thai population[31,32]. Thus our study was ensured thoroughly to preclude potential confounding situations.

As the population study, this study may represent the situation of vitamin D status among HIV infected Thai adults specifically rather than general trend.

Our study re-evaluated the locally prevalent and relevant traditional and HIV-related factors influencing kidney function decline including common first-line ARVs.

Our study focused on glomerular functions of kidney function while there were many kidney function studies about tubular functions. This is the gain of new knowledge from old theme not only for individuals clinically but also for community epidemiologically.

CHAPTER 7
Results

7.1 Study Population

A total of 435 participants were longitudinally observed over median follow-up 30 (IQR:12 – 54) months based on consecutive 6-month interval of follow-ups with eGFR. Participants were 271(62%) men and 164(38%) women. 91 (21%) ,219 (50%) and 125 (29%) participants were vitamin D normal, insufficient and deficient respectively.

131 (30%) had hypertension, 51(11%) had diabetes mellitus, only 5 participants (1%) had gout. 54 (12%) participants were co-infected with hepatitis B virus (HBV) and 6 participants (1%) were co-infected with hepatitis C virus (HCV). Regarding CDC staging, 166 (38%), 186 (43%), and 74 (17%) were documented as A, B and C respectively at baseline.

At baseline, all the participants had no vitamin D supplementations. PIs used in this sample were mainly boosted PIs such as Indinavir.

7.2 Overall Participant Characteristics

Mean age was 45.3 years (±10.4) and mean BMI was23 (±3.3) kg/m^2.Median age was 44.4 (IQR:37.5-53.2) years old. Median serum 25 (OH) D was 22.35 (IQR:17.5-28.4) ng/ml. Median baseline eGFR was 96.5(IQR:83.6-106.4) ml/min/1.73m^2. Median CD 4 count and percentage were 548 (IQR:397-712) cells/ mm^3 and 27 (21-33) %. Median nadir CD4 were 159 (IQR:59-252) cells/ mm^3. Other descriptive results of the sample were median FBS 90(IQR:84-98) mg/dl, median systolic BP 123 (113-132) mmHg, median diastolic BP 77 (IQR:70-83) mmHg, median weight 61.5 (IQR: 54.6-68.6) kg. median height 165(IQR:159-170) cm, median BMI 22.7(IQR:20.7- 24.8) kg/m^2.

7.3 Examination of the relationship between vitamin D and eGFR

During median follow-up 30 (IQR:12 – 54) months, participants (15%) had eGFR declined up to 20% drop of baseline eGFR and 3% participants became eGFR<

60ml/min/1.73m^2 in the end. Regarding primary objective for eGFR decline in any extent, mean eGFR difference of low vitamin D group from vitamin D normal group was -2.25 (95%CI: -5.9, 1.4) *p* 0.226 during univariate analysis while adjusted mean eGFR difference was -0.03 (95%CI: -3.28, 3.23) *p* 0.988 during multivariate analysis.

7.4 Comparison among different vitamin D status

Characteristics between low vitamin D and normal vitamin D groups were shown in Table 1. Generally, low vitamin D group have more participants than the normal vitamin D group.

Between low vitamin D and normal vitamin D groups, there were significant differences in gender distribution, and presence of hepatitis B virus co-infection. However, there were slight differences in presence of hepatitis C virus or diabetes mellitus.

Age, BMI, hypertension, gout, baseline HIV RNA viral load, baseline CD4 count, CD4 nadir, baseline eGFR, serum FBS and follow-up (months) were not significantly different between two groups.

7.5 Identification of Factors associated with eGFR decline

From univariate analysis, mean eGFR differences of the following covariates were as follows from references. Follow-up in months -0.03(95%CI: -0.04, -0.02) *p* < 0.001; age in years -0.70 (95%CI: -0.81, -0.58) *p* < 0.001; being female 2.09 (95%CI:-0.98, 5.20) *p* 0.183;BMI -0.22 (95%CI: -0.48 ,0.03) *p* 0.083;baseline eGFR 0.78 (95%CI: 0.70, 0.85) *p* <0.001; baseline HIV-RNA (log 10 copies/ml) 0.51 (95%CI: -0.01, 1.02) *p* 0.054; diabetes mellitus -11.12 (95%CI: -15.7, -6.6) *p* <0.001; hypertension -9.11 (95%CI: -12.27, -5.95) *p* <0.001; gout -14.11 (95%CI: -28.06, -0.15) *p* 0.048; co-infection with HBV 2.90 (95%CI: -0.98, 6.8) *p* 0.143 ; co-infection with HCV 7.41 (95%CI: -0.59, 15.42) *p* 0.070; CD4% 0.02 (95%CI: -0.06, 0.10) *p* 0.591; CD4 nadir 0.003 (95%CI: -0.009,0.014) *p* 0.631; previous exposure of TDF -0.16 (95%CI: -0.77, 0 .45) *p* 0.608; previous exposure of EFV-0.05 (95%CI: -0.50, 0.40) *p* 0.842 ; previous exposure of PIs -0.64 (95%CI: -1.07, -0.20) *p* 0.004 ; current use of TDF -0.42 (95%CI: -1.38, 0.54) *p* 0.393, current use of EFV4.14

(95%CI: 3.60, 5.22) *p* <0.001; and current use of PIs -0.73 (95%CI: -1.98,0.52) *p* 0.252.

From multivariate analysis, adjusted mean eGFR differences of the following covariates were as follows from references. Follow-up in months -0.07 (95%CI: -0.09, -0.04) *p*< 0.001; age in years -0.20 (95%CI: -0.40, -0.01) *p* 0.042; being female 1.83 (95%CI: -0.79, 4.45) *p* 0.172 ;BMI -0.05 (95%CI: -0.37, 0.26) *p* 0.750 ;baseline eGFR 0.77 (95%CI: 0.67, 0.87) *p* <0.001; baseline HIV-RNA (log 10 copies/ml) -1.87 (95%CI: -4.47, 0.74) *p* 0.161 ; diabetes mellitus -1.98 (95%CI: -5.72, 1.77) *p* 0.301 ; hypertension -1.51 (95%CI: -4.38, 1.36) *p* 0.302; gout -2.19 (95%CI: -11.93, 7.54) *p* 0.659; co-infection with HBV -6.23 (95%CI: -13.28, 0.82) *p* 0.083; co-infection with HCV 5.68 (95%CI: -1.27, 12.62) *p* 0.109; previous exposure of PIs 0.08 (95%CI: -0.25, 0.41) *p* 0.632;current use of EFV 2.87 (95%CI: 1.03, 4.70) *p* 0.002

Therefore, age in years, baseline eGFR, follow-up in months and current use of EFV were significantly associated with eGFR decline. Every year of aging was significantly associated with 0.2 ml/min/1.73m^2 of eGFR decline at *p* value 0.042. Follow-up duration per month was significantly associated with 0.07 ml/min/1.73m^2 of estimated eGFR decline at *p* value less than 0.001. Every ml/min/1.73m^2 of baseline eGFR was significantly associated with 0.77 ml/min/1.73m^2 of eGFR preservation at *p* value less than 0.001. Presence of current use of EFV was significantly associated with 2.87 ml/min/1.73m^2 of eGFR preservation at *p* value at 0.002.

7.5 Other Analyses

With a significant interaction between BMI and vitamin D concentration (*p* = 0. 02), the adjusted mean predictions of eGFR change at 24 months for patients with BMI ≥25kg/m^2 and deficient, insufficient and normal vitamin D were 89. 8 (88. 3 – 91. 4), 91. 2 (90. 1-92.4) and 92. 8 (91. 3-94. 4), respectively. In those with BMI <25kg/m^2 and deficient, insufficient and normal vitamin D, the adjusted mean predictions in eGFR change were 92. 0 (91. 1 – 93. 0), 91. 6 (90. 9-92. 3) and 92. 3 (91. 3-93. 3), respectively. Thus BMI ≥25kg/m^2 might have the effect modification of low vitamin D on kidney function decline.

Table 1. Comparisons of Characteristics among different groups of vitamin D

Variables	Total 435 participants (100%)	Normal Vitamin D 91 participants (21% of total)	Low Vitamin D 344 participants (79% of total)	*p* value
Age in year (baseline)	45.3 (±10.4)	44.1 (±9.7)	45.7 (±10.6)	0.19
BMI (baseline)kg/m^2	23 (±3.3)	23.2 (±3.8)	22.9 (±3.2)	0.13
Male (n, %)	271 (62)	71 (78)	200 (58)	0.005
Female (n, %)	164 (38)	20 (22)	144 (42)	
Hypertension (n, %)	131 (30)	27 (29.7)	104 (30.2)	0.92
Diabetes Mellitus (n, %)	51 (11)	6 (6.6)	45 (13.1)	0.09
Gout (n, %)	5 (1)	1 (1.1)	4 (1.2)	0.59
HBV/HBs Ag (n, %)	54 (12)	17 (18.7)	37 (10.8)	0.04
HCV (n, %)	6 (1)	3(3.3)	3(0.9)	0.08
HIV RNA.log10Copies/ml (baseline)	1.6 (1.3 -1.7)	1.6 (1.3 -1.7)	1.6 (1.3-1.7)	0.55
CD4 count (baseline) cells/mm^3	548 (397-712)	525 (358-670)	555 (408-725)	0.13
CD4 nadir (cells/mm^3)	159 (59-252)	134 (51-240)	167 (67-254)	0.19
eGFR baseline ml/min/1.73m^2	96.54 (83.59 -106.38)	97.18 (84.97-105.74)	96.50 (82.55-107.05)	0.17
Serum Fasting sugar (mg/dl) (baseline)	90 (84-98)	89 (83-96)	91 (84-98)	0.20
Follow-up in months	30 (12-54)	33 (18-54)	30 (12-54)	0.17

Mean & standard deviation (SD); Median & Interquartile range (IQR) for continuous variables;

"n &%" number of participants and percentage for column.

Table 2. For eGFR outcomes (by Generalized Estimating Equations, GEE Models)

Variables (Units)	Univariate			Multivariate		
	β	95%CI	*p* value	β	95%CI	*p* value
Age (years)	-0.70	-0.81, -0.58	<0.001	-0.20	-0.40, -0.01	0.042
Gender (female)	2.09	-0.98, 5.20	0.183	1.83	-0.79, 4.45	0.172
BMI (kg/m^2)	-0.22	-0.48 ,0.03	0.083	-0.05	-0.37, 0.26	0.750
Low Serum 25 (OH)D ng/ml	-2.25	-5.9, 1.4	0.226	-0.03	-3.28, 3.23	0.988
Follow-up (months)	-0.03	-0.04, -0.02	<0.001	-0.07	-0.09, -0.04	<0.001
Baseline eGFR ($ml/min/1.73m^2$)	0.78	0.70, 0.85	<0.001	0.77	0.67, 0.87	<0.001
Diabetes Mellitus	-11.12	-15.7, -6.6	<0.001	-1.98	-5.72, 1.77	0.301
Hypertension	-9.11	-12.27, -5.95	<0.001	-1.51	-4.38, 1.36	0.302
Gout	-14.11	-28.06, -0.15	0.048	-2.19	-11.93, 7.54	0.659
Hepatitis B co-infection	2.90	-0.98, 6.8	0.143	-6.23	-13.28, 0.82	0.083
Hepatitis C co-infection	7.41	-0.59, 15.42	0.070	5.68	-1.27, 12.62	0.109
HIV RNA (log 10copies/ml)	0.51	-0.01, 1.02	0.054	-1.87	-4.47, 0.74	0.161
CD4 %	0.02	-0.06, 0.10	0.591			
CD4 nadir (cells/mm3)	0.003	-0.009,0.014	0.631			
Previous exposure in years						
TDF	-0.16	-0.77, 0 .45	0.608			
EFV	-0.05	-0.50, 0.40	0.842			
PIs	-0.64	-1.07, -0.20	0.004	0.08	-0.25, 0.41	0.632
Presence of Current Use						
TDF	-0.42	-1.38, 0.54	0.393			
EFV	4.14	3.60, 5.22	<0.001	2.87	1.03, 4.70	0.002
PI	-0.73	-1.98,0.52	0.252			

β refers to coefficient (or mean coefficient). This table was to show mean eGFR differences from references as outcomes. Multivariate analysis was for adjusted 13 other covariates.

CHAPTER 8
Discussion

8.1 Relationship between serum 25 (OH)D and eGFR

During median follow-up 30 (IQR:12 – 54) months, participants (15%) had eGFR declined up to 20% drop of baseline eGFR and 3% participants became eGFR< 60ml/min/1.73m^2 in the end. Our primary objective was to test the relationship between low serum 25 (OH)D and eGFR decline of any extent. The association of low vitamin D with eGFR decline were not significant in both univariate and multivariate analyses. This finding is consistent with that of among general population as stated in Damasiewicz MJ et al. where low serum 25 (OH) D is associated with albuminuria but not with eGFR decline[6]. However, our finding matched with the finding for black Americans in Tin et al. However, our non-significant association among HIV-infected Thai patients was different from that of white Americans and Caucasians in Tin et al study. These might be due to racial and geographical differences on eGFR and vitamin D levels[40,43]. Tin et al, an US multicenter HIV cohort showed that white elderly with co-morbidities showed the significant association between low serum 25 (OH) D and rapid eGFR decline. However, younger black Americans who have higher eGFR than white American in their cohort did not prove this association. Regarding serum 1, 25 (OH) 2 D, both showed with rapid decline of eGFR but not statistically significant[7].Their findings were also contradictory to the fact of faster eGFR decline among racial difference of black individuals [5,6]. Their findings might be due to the distribution of age and eGFR across their cohort [7,20]. In similar way, our findings are also different from those of US study. The association between lower serum 25 (OH) D and rapid eGFR decline among white elderly Americans were explained by the possibility of the effect of early manifestation of end organ disease related with the accelerated aging in HIV patients on ART[42]. Conversely, among HIV-infected Thais who were virologically well - suppressed on HAART without end organ disease might not have the significant association between lower serum 25 (OH) D and rapid eGFR decline. This may explain for our current cohort status and our findings. Regarding lack of statistically

significance of the relationship between serum 25 OHD and eGFR in our study, we did rigorous literature review. We also found a similar finding in the different Thai HIV-HBV population as shown in Avihingsanon A et al [25]. Thus, our current study may support the fact that vitamin D level is not independently associated with eGFR decline among HIV-infected Thais who are well-treated and had achieved therapeutic goals on HAART.

Additionally, to be discussed, multivariate analysis in our study is a kind of extension of CKD-EPI equations [31,32]. However, we omitted serum creatinine for collinearity with eGFR and CD4 counts for HIV viral load since univariate analyses.

8.2 Factors associated with eGFR decline

Identifying factors associated with eGFR decline is one of the secondary objectives of the study. After multivariate analysis, baseline eGFR, age in years, follow-up duration in months, current use of EFV were statistically significant. These findings are consistent along with the results from other kidney function studies [25,41,51]Our finding also supports that traditional factors on eGFR decline like age should always be considered even among HIV patients rather than ARV factors alone. Also discussed about the importance of ageing and metabolic complications on eGFR consistently with other papers [33,36,37,42] However, diabetes, hypertension, current use of PIs, and BMI were not significant in our study.[5] The significance of baseline eGFR were consistent with Zhang L, Tin A, et al while lesser significance of baseline HIV RNA viral load was due to well suppression in our cohort[52]. Even though the magnitude of association of follow-up duration were small, they were statistically significant.

Regarding Co-infection with hepatitis B or C viruses were lesser significant in our studies if compared to other studies. This might because of our sample size and median follow-up. Baseline CD4 count and nadir CD4 were not significantly associated eGFR level since univariate analysis in our study. This is consistent with Dao CN et al. [11]

Regarding ARVs, previous exposures of TDF or EFV were not significant even during univariate analyses. Hence our finding reflects, current use may be more

important than previous exposure. TDF, especially duration of TDF might not impact on eGFR significantly which is consistent with a Japanese HIV study[13]. TDF mainly affects tubular functions rather than glomerular functions in renal aspects while TDF also causes hyperparathyroidism and increased bone loss [5,6,44]. A rat model also demonstrated that VDD aggravated TDF nephrotoxicity and induced hypertension and hyperlipidaemia [2]. However, our current study did not prove this finding specifically since TDF have already adjusted for time and tubular functions were also not covered by our current study [44]. PIs are high risk for nephrolithiasis causing stones impacting tubulo-secretory function. Among them, ritonavir has the capacity to boost TDF nephrotoxicity, or tubulopathy. PIs may not impact on eGFR. Consistently, current use of PIs was not significantly associated with eGFR decline in our study. Though Efavirenz causes renal stones affecting tubular function, it may also not impact on eGFR decline. Thus, it may not have effects on glomerular functions decline. This is consistent with our finding of statistically significant in eGFR preservation.

Current use of EFV were positively associated with eGFR decline which might be explained by the effect of boosted PIs. Hepatitis B co-infection association direction was changed from positive to negative in multivariate analysis which might be explained by the possibility of some interactions in the model.

8.3 Comparison of Characteristics among different vitamin D status

According to our data, low vitamin D group have more participants than the normal vitamin D group. Between low vitamin D and normal vitamin D groups, there were significant differences in gender distribution, and presence of hepatitis B virus co-infection. However, there were slight differences in presence of hepatitis C virus or diabetes mellitus. These might be explained by physio-pathological mechanism of vitamin D in addition to sample size differences within groups.[18,25,26]

Age, BMI, hypertension, gout, baseline HIV RNA viral load, baseline CD4 count, CD4 nadir, baseline eGFR, serum FBS and follow-up (months) were not significantly different between two groups.

8.4 Limitations

Our study did not cover for the unmeasured variables such as the important correlates of vitamin D metabolism, such as measures of vitamin D binding protein and parathyroid hormone.[46-48] The inflammatory markers such as TNF alpha, C reactive proteins, gamma interferons, and tubular makers such as urinary beta2microglobulins, urine albumin, serum phosphate measures were not available in our study. The measures of albuminuria, a marker of kidney damage, is an important predictor of kidney function decline.[41]There was also no data about 1,25 (OH)2D in our cohort. Therefore, our study did not prove on renal protection of 1,25 (OH)2D, especially on albuminuria[49]. We did not adjust 1,25 (OH)2D to cope the physiological relationship between serum 25 (OH)D and 1,25 (OH)2D in the model. The one -time measure of serum 25(OH)D as predictors may limit context of vitamin D level over time. However, 25(OH)D has longer half-life and relatively stable concentration than 1,25(OH)2D which has short half-life and may be less stable. The creatinine status in HIV patients because of their muscle wasting may reduce eGFR precision. Although we tried to put ARVs in the model with the clinically-sensible statistical approach on individual ARVs, in our cohort we could not test the boosted effect of PIs to TDF specifically and statistically. However, we evaluated the class-effect of common ARVs on eGFR.

CHAPTER 9
CONCLUSION

Among HIV-infected Thai adults, low vitamin D was not significantly associated with eGFR decline while age in years, baseline eGFR, and follow-up (months) and current use of EFV were statistically significant.

Our study showed the important predictors of eGFR decline among HIV-infected Thai adults. Even though these cannot be generalized, our findings are consistent with the findings of previous studies.

Our participants were on well suppressive therapy and we precluded all possible confounding factors. Thus, aging along with follow-up duration were significantly associated with eGFR decline. Basically, baseline eGFR was also associated with eGFR outcome.

Further studies in larger population with diverse ethnicity or multi-centered studies are warranted. Clinical trials should be done for therapeutic outcome in HIV-infected adult population.

Disclosure

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Two abstracts in the abstract book of 4th Asia Pacific AIDS & Co-infections Conference

Kidney Function Decline Among HIV-infected Thai adults: Is Low Vitamin D is one of the factors?

Kidney Function Decline Among HIV-infected Thai adults: What are Contributing Factors?

Poster abstract

Kidney Function Decline Among HIV-infected Thai adults: Is Low Vitamin D is one of the factors? (updated)

(Notes: Parts of the findings before ARVs adjustment were involved.)

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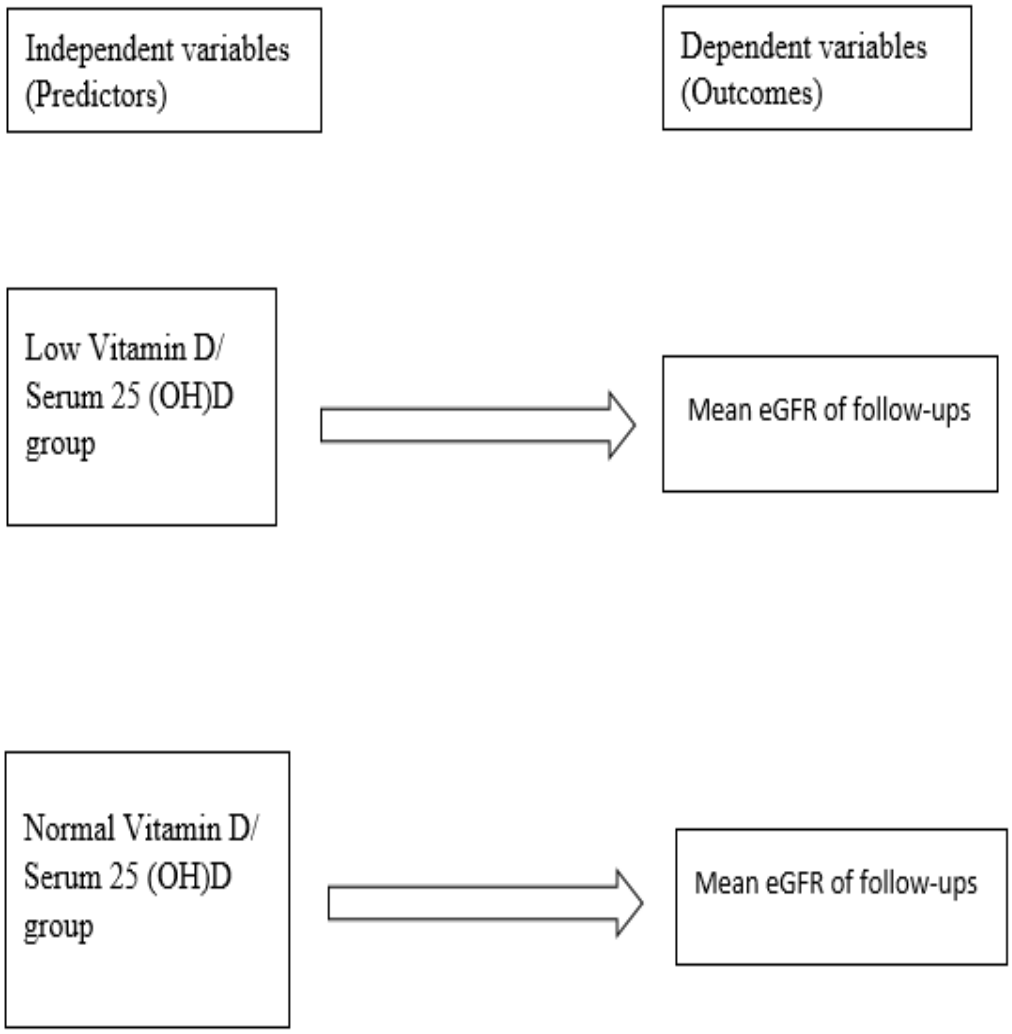
APPENDIX

Appendix 1: Study Design in Focus



Appendix 2: Methods in Concise

Objectives	Description	Outcomes	Statistical Methods
Primary	To exam the relationship between low vitamin D and kidney function decline among HIV-infected adults in Thailand	For association and magnitude of association	Generalized estimating equation (GEE)
Secondary	To compare the characteristics among the different groups of vitamin D level of HIV-infected adults in Thailand		Descriptive study
Secondary	To identify the significant contributing factors to kidney function decline among HIV-infected adults in Thailand		Generalized estimating equation (GEE)

Appendix 3: Case Record Form

Low Vitamin D and Kidney Function Decline among HIV infected adults in Thailand (Project site: HIVNAT, Bangkok, Thailand)

IRB No. ☐☐☐☐☐☐☐

Date of Visit: ☐☐ ☐☐ ☐☐☐☐

Demographic Data & Eligibility Criteria

Cohort ID: ☐☐☐☐☐☐

Date of Birth: ☐☐ ☐☐ ☐☐☐☐ Age: ☐☐ years completed

Gender: Male ☐ Female ☐

Race: Thai ☐ Non-Thai Asian ☐ Not specified/ unreported ☐

Marital Status: Single ☐ married ☐ separate ☐ divorce ☐ living together ☐

Education: illiterate ☐ literate/ primary ☐ secondary /high ☐ college /University ☐

History: Hypertension ☐ Diabetes Mellitus ☐ kidney stones ☐ UTI ☐ obstructive uropathy ☐ gout ☐

Concurrent illness: diabetes ☐ hypertension ☐ gout ☐ kidney stones ☐ obstructive uropathy ☐ UTI ☐

Other diseases: bone ☐ endocrine ☐ kidney ☐ metabolic ☐

Family history: kidney failure ☐ hypertension ☐ diabetes ☐

Previous or Current Drug History: drugs causing hypovitaminosis D ☐ Drugs impaired renal functions ☐ use of OHA ☐ antihypertensives ☐ antigout drugs ☐ traditional medicine use ☐

History on habits: dietary fibers ☐ well intake of water and output of urine ☐

; regular exercise ☐

HIV history: Duration of HIV _____years; Duration of ART: _____years; types of ARV: _____; compliance: Yes /No

Informed consent was obtained

1. From the participant or legally authorized person_____
2. Through Study coordinator _____
3. Witnessed by _____
4. On the date of _____
5. At the venue of _____

Type of visit: Baseline ☐ Follow up ☐ Date of Visit ☐☐ ☐☐ ☐☐☐☐

Clinical Data

Vital signs: BP ☐☐☐ / ☐☐ mmHg; HR ☐☐☐ /min; RR ☐☐ /min;

Body Temperature: ☐☐.☐ ºC

BMI: ☐☐.☐ kg/m^2

Investigations

ECG: normal ☐ abnormal ☐ : please specify_____

AXR/ USG (ABD): normal ☐ abnormal ☐ : please specify_____

Urinalysis: normal ☐ abnormal ☐ : please specify _____

Main Laboratory data

Serum25(OH)D: 0☐ 1☐ 2☐ level _____ ng/ml

Plasma RNA HIV1: _____ copies/ml

CD 4count: _____cells / mm^3

Serum creatinine: _____ mg/dl

Fasting sugar level: _____ mg/dl

Simplified Assessment Chart for eligibility of participants for the study

Disease	Duration	Medication	Duration of Medication	route	dose	Frequ-ency

Inclusion criteria	Y/N	Exclusion Criteria	Y/N
Must be completed 18 when enrolled in cohort		Patients with other renal/ HIV spectrum of renal diseases	
Must be virological well suppressed (plasma RNA <400 copies/ml within past 6 months)		Patients with metabolic/ endocrine/Bone diseases	
Must be on ART		Patients with drugs causing VDD/CKD	
eGFR must be equal and over 60 ml/min/1.73m^2.		Patients with contributing factors for VDD/CKD	

Appendix 4: Institutional Review Board‟s Approval (Thai)

COA No. 252/2019

IRB No. 037/62

คณะกรรมการพิจารณาจริยธรรมการวิจัย

คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

1873 ถ.พระราม 4 เขตปทุมวัน กรุงเทพฯ 10330 โทร. 0-2256-4493

เอกสารรับรองโครงการวิจัย

คณะกรรมการจริยธรรมการวิจัยในคน คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ดำเนินการให้การรับรองโครงการวิจัยตามแนวทางหลักจริยธรรมการวิจัยในคนที่เป็นมาตรฐานสากลได้แก่ Declaration of Helsinki, The Belmont Report, CIOMS Guideline และ International Conference on Harmonization in Good Clinical Practice หรือ ICH-GCP

ชื่อโครงการ : วิตามินดีที่ต่ำและการลดลงของการทำงานของไตในผู้ป่วยไทยที่ติดเชื้อเอชไอวี

เลขที่โครงการวิจัย :

ผู้วิจัยหลัก : MR. WIN HLAING THAN

สังกัดหน่วยงาน : วท.ม. สาขาวิทยาศาสตร์คลินิก (นานาชาติ) คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

วิธีทบทวน : แบบเร่งด่วน

รายงานความก้าวหน้า : ส่งรายงานความก้าวหน้าอย่างน้อย 1 ครั้ง/ปี หรือส่งรายงานฉบับสมบูรณ์หากดำเนินโครงการเสร็จสิ้นก่อน 1 ปี

เอกสารรับรอง :

1. โครงร่างการวิจัย Version 1.2 (22/2/2019)
2. โครงการวิจัยฉบับย่อ Version 1 Date 18th December, 2018
3. Curriculum Vitae and GCP Training
   - Mr. WIN HLAING THAN
   - Asst. Prof. Opass Putcharoen, MD., MSc.
   - Dr. Anchalee Avihingsanon, MD.

ลงนาม .....

(ศาสตราจารย์กิตติคุณแพทย์หญิงชาดา สืบหลินวงศ์)

ประธาน

คณะกรรมการพิจารณาจริยธรรมการวิจัย

ลงนาม .....

(ผู้ช่วยศาสตราจารย์ ดร.พญ.ประภาพรรณ รัชตะปีติ)

กรรมการและเลขานุการ

คณะกรรมการพิจารณาจริยธรรมการวิจัย

วันที่รับรอง : 4 มีนาคม 2562

วันหมดอายุ : 3 มีนาคม 2563

ทั้งนี้ การรับรองนี้มีเงื่อนไขดังที่ระบุไว้ด้านหลังทุกข้อ (ดูด้านหลังของเอกสารรับรองโครงการวิจัย)

Appendix 5: Institutional Review Board‟s Approval (English)

COA No. 252/2019

IRB No. 037/62

INSTITUTIONAL REVIEW BOARD

Faculty of Medicine, Chulalongkorn University

1873 Rama 4 Road, Patumwan, Bangkok 10330, Thailand, Tel 662-256-4493

Certificate of Approval

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, has approved the following study which is to be carried out in compliance with the international guidelines for human research protection as Declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

Study Title : Low vitamin D and kidney function decline among HIV infected adults in Thailand.

Study Code : -

Principal Investigator : Mr. WIN HLAING THAN

Affiliation of PI : M.Sc. in Clinical Sciences, (International Program), Faculty of Medicine, Chulalongkorn University.

Review Method : Expedited

Continuing Report : At least once annually or submit the final report if finished.

Document Reviewed :

1. Research Proposal Version 1.2 (22/2/2019)
2. Protocol Synopsis Version 1 Date 18th December, 2018
3. Curriculum Vitae and GCP Training
   - Mr. WIN HLAING THAN
     Asst. Prof. Opass Putcharoen, MD., MSc.
   - Dr. Anchalee Avihingsanon, MD.

Signature:..... Signature:.....

(Emeritus Professor Tada Sueblinvong MD) (Assistant Professor Prapapan Rajatapiti MD, PhD)

Chairperson Member and Secretary

The Institutional Review Board The Institutional Review Board

Date of Approval : March 4, 2019

Approval Expire Date : March 3, 2020

Approval granted is subject to the following conditions: (see back of this Certificate)

Appendix 6: Multivariate analysis for Mean eGFR differences

GEE population-averaged model — Number of obs = 1,087
Group variable: patno — Number of groups = 244
Link: identity — Obs per group:
Family: Gaussian — min = 1
Correlation: exchangeable — avg = 4.5
max = 14
Wald chi2(14) = 484.75
Scale parameter: 119.5966 — Prob > chi2 = 0.0000

eGFR	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
m	-.0682066	.0135586	-5.03	0.000	-.0947809	-.0416323
lowD	-.025263	1.661171	-0.02	0.988	-3.281097	3.230571
female	1.826484	1.336322	1.37	0.172	-.7926592	4.445626
AGE	-.2029119	.0997117	-2.03	0.042	-.3983432	-.0074805
bmi	-.0510255	.1602211	-0.32	0.750	-.365053	.263002
logvl	-1.866016	1.330767	-1.40	0.161	-4.474271	.7422394
first_eGFR	.7735564	.050475	15.33	0.000	.6746272	.8724855
diabetes	-1.975721	1.910466	-1.03	0.301	-5.720166	1.768724
hypertension	-1.508707	1.462967	-1.03	0.302	-4.37607	1.358656
GOUT	-2.191713	4.966927	-0.44	0.659	-11.92671	7.543286
hbv	-6.226526	3.596563	-1.73	0.083	-13.27566	.8226067
hcv	5.676232	3.542363	1.60	0.109	-1.266673	12.61914
yearPIbeforeBL	.0810229	.1694231	0.48	0.632	-.2510402	.4130861
efv_exposed_timeupdate	2.867129	.9371518	3.06	0.002	1.030345	4.703913
_cons	33.02324	9.335103	3.54	0.000	14.72678	51.31971

Variables: m for follow-up (months); lowD for low vitamin D group; female for being female; AGE for baseline age of participants, logvl for baseline HIV RNA load in log 10 copies/ml; first_eGFR for baseline eGFR, diabetes for diabetes mellitus, hypertension for hypertension; GOUT for gout, hbv for Hepatitis B virus co-infection; hcv for hepatitis C virus co-infection; yearPIbeforeBL for previous exposure of Protease inhibitors(PIs) before baseline (in years); efv_exposed_timeupdate for presence of current use of efavirenz (EFV), _cons for constant.

Bibliography

Name: Win Hlaing Than

Date of Birth: 1st October 1988

Place of Birth: Mandalay, Myanmar

Institution Attended: University of Medicine-Mandalay, Myanmar

Degree Obtained: M.B.,B.S (5th February, 2012)

Membership: Myanmar Medical Association

Professional Interests: Physician Scientist; clinical practice and research

Areas of Interests:

Metabolic complications, SGLT2 inhibitors, Renal function markers

Active areas:

Micronutrients, Vitamin D, Renal function, HIV

Skills and expertise:

Clinical practice in internal medicine, continuing care in family medicine

Cross-sectional and cohort analysis, clinical study, population study, etc.

Multi-lingual: English, Mandarin, Chinese Dialect, Myanmar, limited Thai.

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